In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-227V

(Filed: February 4, 2020)

BERNARD HALVERSON, *EXECUTOR of the ESTATE of SUSAN HALVERSON, deceased,*	*	To Be Published
Petitioner,	*	High-Dose Influenza ("Fluzone"); Vaccine; Cardiac Arrest; Death; Significant Aggravation
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Jerry Lindheim, Esq., Locks Law Firm, Philadelphia, PA, for petitioner.
Lisa Watts, Esq., U.S. Dept. of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On March 4, 2015, Bernard Halverson ("Mr. Halverson" or "petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*[2] ("Vaccine Act" or "Program") as executor of the estate of his late wife, Susan Halverson ("Mrs. Halverson"). Petitioner alleges that Mrs. Halverson received a high-dose

[1] This Ruling has been designated "to be published," which means I am directing it to be posted on the Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). **This means the Ruling will available to anyone with access to the internet.** However, the parties may object to the Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Ruling will be available to the public. *Id*.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

seasonal influenza vaccine ("Fluzone") on January 9, 2014, which caused cardiac arrest and her subsequent death on January 13, 2014. *See* Petition ("Pet."), ECF No. 1. Alternatively, petitioner claims that the flu vaccine significantly aggravated Mrs. Halverson's ischemic heart disease, leading to her death.

As explained fully and in detail below, petitioner has established that the high-dose flu vaccine received by Mrs. Halverson was a substantial factor in her cardiac arrest and subsequent death.

I. Procedural History

The petition was filed on March 4, 2015. ECF No. 1. On April 2, 2015, petitioner filed Mrs. Halverson's death certificate and medical records, as well as proof that he had been appointed the executor of her estate, as Petitioner's Exhibits ("Pet. Ex.") 1-9.[3] ECF No. 7. These exhibits were later stricken from the record as incorrectly filed. *See* Non-PDF Order, issued Aug. 25, 2016.

The initial status conference was held on May 7, 2015. Petitioner was ordered to file additional medical records. Scheduling Order, ECF No. 8.

On July 16, 2015, respondent filed his Rule 4(c) Report ("Resp. Rpt."), stating that this case was not appropriate for compensation. Resp. Rpt., ECF No. 13. More specifically, respondent noted that Mrs. Halverson's cardiologist had previously discussed her risk of sudden cardiac death related to ventricular tachycardia, which resulted in Mrs. Halverson having an automatic implantable cardioverter defibrillator ("AICD") placed. *Id*. at 3. Respondent submitted that Mrs. Halverson's death was the result of her longstanding heart disease which was marked by worsening cardiac function over the previous year, and required placement of the AICD. *Id*. at 7.

Following a status conference on November 12, 2015,[4] petitioner was ordered to file expert reports. Scheduling Order, ECF No. 27. Petitioner filed expert reports from Dr. Robert Stark and Dr. Gourang Patel on January 28, 2016. Pet. Ex. 10-11, ECF No. 30.

On June 14, 2016, respondent filed an expert report from Dr. Joseph Murphy. Resp. Ex. A-B, ECF No. 33. Respondent filed an addendum to Dr. Murphy's report on June 16, 2016. Resp. Ex. C, ECF No. 34.

Petitioner filed two additional reports from Dr. Stark on July 5 and 8, 2016. Pet. Ex. 19, ECF No. 35, 38;[5] Pet. Ex. 20, ECF No. 37.

Respondent filed an expert report from Dr. Noel Rose on July 6, 2016 and supporting medical literature on July 11, 2016. Resp. Ex. D-E, ECF No. 36; Resp. Ex. F-N, ECF No. 39.

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[3] Petitioner submitted an affidavit that stated nothing more than he had not filed a civil action in this matter. *See* Pet. Ex. 5.

[4] This case was reassigned to me on October 19, 2015. ECF No. 21.

[5] Dr. Stark's report, Pet. Ex. 19, was filed twice and occurs on the docket at ECF Nos. 35 and 38.

Petitioner filed medical literature on July 12, 2016, as Pet. Ex. B-L. ECF No. 40. These exhibits were later stricken due to improper filing. *See* Non-PDF Order, issued Aug. 25, 2016.

A status conference was held on July 14, 2016. Scheduling Order, ECF No. 41. During the conference, it was "clarified that petitioner's experts claim that [Mrs. Halverson's] death was not necessarily caused by the vaccine, but rather that the vaccine significantly aggravated petitioner's pre-morbidities and contributed to petitioner's eventual death." *Id*. at 1. Respondent requested the opportunity for supplemental reports to "flesh out" his response to petitioner's significant aggravation claim. *Id*. Respondent was ordered to file supplemental expert reports by September 12, 2016. *Id*. at 2.

Respondent filed a second report from Dr. Murphy and supporting medical literature on August 3, 2016. Resp. Ex. O-U, ECF No. 42.

Petitioner filed a Motion to Strike Pet. Ex. 1-14 and his supporting medical literature, which was filed as "Medical Exhibits A-L," due to improper filing. *See* Motion to Strike, ECF No. 43. This Motion was granted. Non-PDF Order, issued Aug. 25, 2016. Petitioner properly filed Pet. Ex. 1-16 on September 7, 2016. *See* Pet. Ex. 1-9, ECF No. 44; Pet. Ex. 10-16, ECF No. 45.

Respondent filed an additional expert report from Dr. Rose on September 9, 2016. Resp. Ex. V, ECF No. 46.

Petitioner filed supplemental expert reports from Dr. Stark and Dr. Patel on September 13, 2016. Pet. Ex. 17-23, ECF No. 47.

A Rule 5 status conference was held on December 21, 2016. Scheduling Order, ECF No. 48. I summarized the medical records as follows:

> …Ms. [sic] Halverson, then 65 years old, had a complicated medical history which included but was not limited to congestive heart failure, insulin dependent diabetes, renal failure, hypertension and left ventricular systolic dysfunction. Mrs. Halverson's health declined in 2013 due to her heart problems, and in September of 2013 she underwent implantation of a biventricular cardioverter defibrillator (ICD) to avoid the risk of sudden cardiac death. Mrs. Halverson was noted to be doing well in the months that followed the implantation of the defibrillator. On January 9, 2014, Mrs. Halverson presented to her doctor with complaints of congestion, ears feeling clogged, loose cough, and scratchy throat….She was administered the Fluzone high dose vaccine intramuscularly. In the days that followed, Mrs. Halverson was noted to be weaker, with cough and congestion, decreased food and water intake, and shortness of breath. On January 13, 2014, Mrs. Halverson went to get dressed so that her husband could take her to the emergency room. She apparently went into cardiac arrest. According to her husband, the internal defibrillator's warning system did not sound. Attempts to resuscitate her were unsuccessful and Mrs. Halverson passed away at that time.

Id. at 1. Following that recitation, I noted that no blood work was performed on Mrs. Halverson in the course of her emergency treatment, and no autopsy was performed after her death. *Id*. The

parties were encouraged to settle this matter, but were unable to reach a resolution. *Id*.; Joint Status Report, ECF No. 49.

An entitlement hearing was initially scheduled for November 5 and 6, 2018, to be held in Washington, D.C. Prehearing Order, ECF No. 51. It was later rescheduled to November 6 and 7, 2018. Scheduling Order, ECF No. 58.

The parties elected not to file post-hearing briefs. *See* Transcript ("Tr.") 313-14.

This matter is ripe for decision.

II. Overview of Heart Function

The heart is made up of four chambers. *Heart*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 825 (32nd ed. 2012) [hereinafter "DORLAND'S"]. The upper two chambers are called the atria and the lower two chambers are called the ventricles. *Id*. The heart functions as a two-part pump. MARY M. CANOBBIO, CARDIOVASCULAR DISORDERS 4 (William G. Brottmiller ed., 1st ed. 1990) [hereinafter "CANOBBIO"]. The sinoatrial ("SA") node conducts an electrical impulse which causes both atria to contract, forcing blood from the atria into the ventricles. *Id*. at 6, 15. The atrioventricular ("AV") node, located in the floor of the right atrium, receives the electrical impulse and spreads it to the ventricles. *Id*. at 15. The ventricles then contract, pushing blood out to the body. *Id*. at 6. The chambers of the heart only contract if stimulated by electrical activity. GAIL WALRAVEN, BASIC ARRHYTHMIAS 2 (3rd ed. 1992) [hereinafter "WALRAVEN"].

If another conduction site in the heart discharges electrical impulses at a faster-than-normal rate, it can override the SA node and take over the pacemaking function for the heart. WALRAVEN at 8. The process of another conduction site taking over as pacemaker is called "irritability." *Id*. Increased irritability to either the atria or the ventricles can result in increased electrical impulses. This can cause "fibrillation," where the chamber "quivers ineffectively" rather than contracting fully. *Id*. at 100. Atrial fibrillation ("Afib") causes the ventricular rhythm to be "grossly irregular," but Afib can be managed via medication. *Id*. at 100-01; CANOBBIO at 67. In contrast, ventricular fibrillation ("Vfib") is a lethal arrhythmia because the heart rhythm becomes chaotic and ineffective. WALRAVEN at 191.

Afib occurring alone can be unrecognizable or very symptomatic. HURST'S THE HEART 824 (Valentin Furster et al. eds., 10th ed. 2001) [hereinafter "HURST'S"]. However, when Afib occurs in conjunction with other cardiac conditions, such as mitral or aortic stenosis, restrictive cardiomyopathies, or advanced left ventricular dysfunction, Afib may cause severe hemodynamic deterioration. *Id*. Afib can be caused by mitral or aortic stenosis or regurgitation, hypertension, coronary heart disease, cardiomyopathy, atrial septal defect, or pericarditis; it can also occur secondary to left or right ventricular overload. *Id*. at 826. People with Afib are five times more likely to have a stroke than people who do not have Afib. *Id*. at 828. Chronic recurrent atrial fibrillation may require an automatic implantable cardioverter defibrillator ("AICD"). *Id*. at 828.

Vfib occurs most commonly in the setting of acute ischemic events, like myocardial infarction, or in advanced chronic ischemic heart disease. HURST'S at 852. It is the cause of death

in 25 to 50 percent of all cardiac fatalities. *Id*. Vfib may also develop during ischemia caused by coronary artery spasm or atrial fibrillation with rapid ventricular responses. *Id*. A particularly high-risk setting for Vfib is acute myocardial infarction with right or left bundle-branch block. *Id*. Vfib is a life-threatening condition that requires emergency defibrillation. *Id*. at 853.

Chronic Vfib requires implantation of an AICD. HURST'S at 854. An AICD is implanted in the chest and connected to the heart via electrodes. *Id*. at 950. The AICD detects abnormal heart rhythms, such as Vfib, and defibrillates the heart via an electric shock within 10 to 15 seconds of detecting Vfib. *Id*. at 947. AICDs are very effective in terminating ventricular tachydysrhythmias; in a large-scale study over five years, approximately 98% of episodes of Vfib were detected and successfully terminated. *Id*. at 1037. However, the overall mortality in patients with AICDs remains high at approximately 22% because most AICD recipients already have heart failure. *Id*. at 954; Resp. Ex. S at 42.[6] The AICD may help the patient survive an episode of Vfib, but the patient may still die due to other cardiac problems. HURST'S at 954.

Factors that contribute to Afib and Vfib are smoking, excessive caffeine, obesity, high blood pressure, diabetes, high alcohol intake, hyperthyroidism, coronary heart disease, and heart failure. *See* CANOBBIO at 72; Resp. Ex. V, Tab 6 at 1, 4.[7]

Myocardial infarction, commonly referred to as heart attack, and cardiac arrest are very different. In a heart attack, a blocked artery prevents blood from reaching sections of the heart; if it is not opened quickly, the part of the heart normally nourished by that artery begins to die. *See* CONOBBIO at 81. Symptoms can include chest pain, shortness of breath, dizziness, nausea and vomiting, weakness, gastrointestinal distress, and/or low-grade fever. *Id*. at 85-86. Symptoms can be immediate or start slowly and persist for hours, days, or weeks before a heart attack. HURST'S at 1278-79.

Cardiac arrest is the sudden cessation of the pumping function of the heart; it signifies either ventricular fibrillation or ventricular standstill. *Cardiac arrest*, DORLAND'S at 133. It is characterized by abrupt loss of consciousness that uniformly leads to death without immediate intervention. HURST'S at 1030. Cardiac arrest can occur as a result of the electrophysiologic effects of acute ischemia, acute changes in mechanoelectrical feedback, or changes in autonomic innervation of the heart. *Id*. at 1022-23. Approximately 70% of patients who have cardiac arrest suffer from Vfib; many also have coronary artery disease or other underlying structural heart disease. *Id*.

There are increased risks of cerebrovascular and cardiovascular events following upper respiratory tract infections like influenza. Resp. Ex. K at 8-10.[8] Potential adverse events include

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[6] Steve E. Phurrough et al., *Decision Memo for Implantable Defibrillators (CAG-00157R3)*, CMS.GOV (Jan. 27, 2005) (printed July 25, 2016), filed as "Resp. Ex. S."

[7] Darae Ko et al., *Atrial Fibrillation in Women: Epidemiology, Pathophysiology, Presentation, and Prognosis*, 13 NAT. REV. CARDIOL. 321-32 (2016), filed as "Resp. Ex. V, Tab 6."

[8] Kristin L. Nichol et al., *Influenza Vaccination and Reduction in Hospitalizations for Cardiac Disease and Stroke among the Elderly*, 348 N. ENGL. J. MED. 14: 1322-32 (2003), filed as "Resp. Ex. K."

alterations in circulating clotting factors, platelet aggregation and lysis, concentrations of inflammatory-response proteins, and alterations in cytokine concentrations. *Id*. These changes might enhance thrombotic tendencies, impair vasodilation, or cause endothelial injury. *Id*. Influenza vaccines are recommended for persons over the age of 65 and for anyone with a high-risk medical condition in order to reduce the risk of hospitalization for cardiac and cerebrovascular causes. *Id*. at 10. However, subspecialists are less likely than generalists to recommend influenza vaccination to their high-risk patients, and only half of cardiology practices in the U.S. stock influenza vaccine compared to 70% of primary care practices. *Id*.; Resp. Ex. L at 4.[9]

III. Medical History

A. Mrs. Halverson's Health Prior to Receiving Fluzone

Mrs. Halverson was born on December 14, 1948. Pet. Ex. 3 at 2. Her father suffered from diabetes and heart disease before passing away at age 65, while her mother had heart disease and hypertensive disorder and passed away at age 62. *Id*. At the time of her death, Mrs. Halverson and her husband, the petitioner, had been married for almost 44 years. Tr. 8.

Mrs. Halverson had a complicated medical history. At the time of her death, her chronic conditions included insulin-dependent diabetes, stage IV chronic kidney disease, hypertension, hyperlipidemia, hypothyroidism, anemia, obesity, left bundle branch block,[10] ventricular tachycardia, ischemic heart disease, occasional palpitations, and congestive heart failure with left ventricular diastolic dysfunction (NYHA class II).[11] *See* Pet. Ex. 3 at 2-7; Pet. Ex. 4 at 7, 11; Pet. Ex. 7 at 1, 5.

Mrs. Halverson's past surgical history included a vitrectomy in 1986, a 1987 repair of an atrial septal defect ("ASD") that had existed since childhood, orthopedic surgeries on her left palm in 1994 and on both shoulders in 1996, and cataract surgeries in 2003 and 2004. Pet. Ex. 3 at 2. In 2000, she developed complete heart block and underwent placement of a permanent pacemaker; she required a second procedure in 2001 due to lead dislodgement and later had multiple generator changes. Pet. Ex. 7 at 41, 104. Mrs. Halverson was a smoker for 25 years but quit in or around 2004. Pet. Ex. 3 at 3.

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[9] Matthew M. Davis et al., *Influenza Vaccination as Secondary Prevention for Cardiovascular Disease*, 48 J. AM. COLL. CARDIOL. 7: 1498-1502 (2006), filed as "Resp. Ex. L."

[10] "Left bundle branch" refers to the left branch of the bundle of His, "a small band of atypical cardiac muscle fibers" which "propagates the atrial contract rhythm to the ventricles." *Bundle of His*, DORLAND'S at 260 The left bundle branch transmits the atrial contraction rhythm from the AV node to the left ventricle. The interruption of the left bundle branch can cause heart block. *Bundle branch, id*. at 248.

[11] "NYHA class II" refers to the New York Heart Association classification, a functional and therapeutic classification for prescription of physical activity for cardiac patients. A person who falls into Class II has a slight limitation of activity, with symptoms on moderate or normal exertion. *New York Heart Association (NHYA) c.*, DORLAND'S at 369.

In 2008, Mrs. Halverson was assessed for ventricular systolic dysfunction due to a high rate of ventricular episodes. Pet. Ex. 7 at 28. She had experienced frequent episodes of palpitations without chest pain or lightheadedness but sometimes accompanied by shortness of breath. *Id*. Her cardiologist, Dr. Arluck, concluded that she had idiopathic ventricular tachycardia in the absence of left ventricular systolic dysfunction or severe ischemic heart disease that did not warrant suppression for prevention of sudden cardiac death at that time. *Id*. at 28-29.

In 2009, Mrs. Halverson's pacemaker check showed runs of non-sustained ventricular tachycardia ("NSVT").[12] Pet. Ex. 6 at 35-36; Pet. Ex. 7 at 26-27. Dr. Arluck noted a concern for high estimated right ventricular systolic pressure but did not suggest immediate action to address it. *Id*.

On April 9, 2010, Mrs. Halverson presented to Dr. Arluck emergently. Pet. Ex. 4 at 53-54; Pet. Ex. 6 at 29-30; Pet. Ex. 7 at 20-21. Three days before, she had called Dr. Arluck, complaining of extreme lightheadedness ongoing for four or five days. *Id*. He instructed her to "hold Captopril," and her dizziness resolved. *Id*. It was noted that Mrs. Halverson had a "fairly brittle cardiovascular system," and with a bit of excess fluid she would have symptoms of congestion. *Id*. She also had diabetic proteinuria. *Id*.

Blood work throughout 2010 and onward showed high glucose, BUN, and creatinine, with low eGFR, sodium, and chloride. Pet. Ex. 4 at 20-22, 33-36, 41-42, 46, 48, 51-52, 57; Pet. Ex. 6 at 44-49; Pet. Ex. 8 at 157- Pet. Ex. 8 at 16, 17, 51, 60, 61. She also had high B-Type natriuretic peptide ("BNP"). Pet. Ex. 4 at 51. At times, she had low TSH and high hemoglobin A1C. Pet. Ex. 4 at 33, 34, 42, 48; Pet. Ex. 6 at 45, 47, 49; Pet. Ex. 7 at 158, 160.

By May 11, 2011, Dr. Villorani noted that Mrs. Halverson's kidney function had declined and changed her diagnosis to stage IV chronic kidney disease. Pet. Ex. 4 at 37-38; Pet. Ex. 8 at 91-92. She also had uncontrolled anemia. *Id*. She was referred for pre-dialysis education. *Id*. By November of 2011, she was referred for dialysis training. Pet. Ex. 4 at 32.

In April of 2012, Mrs. Halverson underwent pacemaker explant and replacement. Pet. Ex. 4 at 27.

Mrs. Halverson routinely presented for her follow-up visits. *See generally* Pet. Ex. 3; Pet. Ex. 4; Pet. Ex. 6; Pet. Ex. 7.

On April 26, 2013, Mrs. Halverson presented to Dr. Arluck emergently with a four-week history of dyspnea on minimal exertion, non-productive cough, orthopnea, nocturnal dyspnea, chest aching, and two weeks of edema with increased abdominal girth. Pet. Ex. 6 at 5; Pet. Ex. 7 1. She reported snoring and waking up exhausted. Pet. Ex. 6 at 7; Pet. Ex. 7 at 3. Her active medical problems included type I diabetes, hypertension, hyperlipidemia, congestive heart failure, renal injury secondary to diabetes, orthostatic hypotension, shortness of breath, paroxysmal ventricular tachycardia, and hypothyroidism. *Id*. She was noted to have decompensated congestive heart

[12] Non-sustained ventricular tachycardia, or NSVT, is an abnormally rapid ventricular rhythm that terminates spontaneously within 30 seconds and does not result in the heart's failure to function. *Nonsustained ventricular tachycardia*, DORLAND'S at 1867; *ventricular tachycardia, id*. at 1868.

failure. *Id*. Dr. Arluck ordered several tests, including an echocardiogram, chest x-ray, basic metabolic panel ("BMP"), BNP, and a nuclear stress test. *Id*. Bloodwork from this appointment showed high glucose, BUN, creatinine, and BNP, and low eGFR, sodium, and chloride. Pet. Ex. 6 at 43.

An echocardiogram was performed on May 14, 2013 and showed the left ventricle had moderately to severely depressed systolic function and an estimated ejection fraction[13] of 25 to 35%. Pet. Ex. 4 at 7; Pet. Ex. 6 at 78; Pet. Ex. 7 at 87, 150. Mrs. Halverson had abnormal left ventricular diastolic function with a restrictive pattern, suggesting elevated left ventricle diastolic pressure. *Id*. Her right ventricle had normal systolic function but a pressure overload pattern. Pet. Ex. 4 at 8; Pet. Ex. 6 at 79; Pet. Ex. 7 at 88, 151. She had mild tricuspid regurgitation and abnormal septal motion, with right ventricular pacing, right bundle branch block, or right ventricular volume overload. *Id*.

On May 17, 2013, Mrs. Halverson underwent Regadenoson Cardiolite Perfusion Imaging with Gating. Pet. Ex. 4 at 5-6; Pet. Ex. 6 at 82-83; Pet. Ex. 7 at 94-95, 148-49. She did not have ECG changes or pain with stress, but premature ventricular contractions were observed with exercise. *Id*. She did not have any ischemia. *Id*. Her left ventricular systolic function appeared to be moderately to severely depressed, and she had prominent right ventricular uptake. *Id*. It was noted that accuracy of the measured ejection fraction is diminished in patients with ventricular paced rhythm. *Id*.

Blood work was performed on May 22, 2013, and showed low WBC, RBC, hemoglobin, hematocrit, MCHC, eGFR, sodium, and chloride, and high glucose, BUN, creatinine, and BNP. Pet. Ex. 8 at 13-14.

At her May 28, 2013 visit with Dr. Arluck, Mrs. Halverson was noted to have decompensated congestive heart failure with continued weakness, fatigue, and dyspnea. Pet. Ex. 6 at 9; Pet. Ex. 7 at 5. The potential for sudden cardiac death related to NSVT and decreased ejection fraction was discussed. Pet. Ex. 6 at 11-12; Pet. Ex. 7 at 7-8. Dr. Arluck noted that she was a candidate for an AICD and recommended a consultation with Dr. Bullinga regarding the replacement of her pacemaker. *Id*. She was instructed to continue with a healthy diet and appropriate activity, to continue prescribed medications, and to monitor her renal function and electrolytes closely. *Id*.

In July of 2013, Mrs. Halverson continued to experience fatigue, dizziness, increased urination, numbness of feet, and shortness of breath when walking and lying down. Pet. Ex. 3 at 15. She was not seeing an eye doctor yearly and was not taking her blood pressure medications as directed because of side effects; furosemide was decreased due to lightheadedness and low blood pressure readings. *Id*. Blood work performed at that time showed low WBC, platelets, eGFR,

[13] The ejection fraction is a measurement of the percentage of blood leaving the ventricle each time the heart contracts. It is usually only measured in the left ventricle. An ejection fraction of 55% or higher is considered normal; 50% or lower is considered reduced though experts vary and consider 50% borderline. Rekha Mankad, *Ejection fraction: What does it measure?*, MAYO CLINIC (July 2, 2019), https://www.mayoclinic.org/ejection-fraction/expert-answers/faq-20058286

sodium, and chloride, and high glucose, BUN, creatinine, BNP, and hemoglobin A1C. Pet. Ex. 6 at 41-42; Pet. Ex. 7 at 161-62; Pet. Ex. 8 at 11-12.

On July 30, 2013, Mrs. Halverson returned to Dr. Arluck for follow-up of congestive heart failure and left ventricular systolic dysfunction. Pet. Ex. 6 at 14; Pet. Ex. 7 at 9. She reported that she had an appointment with Dr. Bullinga scheduled for August 7 for consideration of an AICD. *Id*. She had lost 24 pounds since presenting with congestive heart failure. Pet. Ex. 6 at 17; Pet. Ex. 7 at 12. She would need a repeat assessment of her left ventricular systolic function, most likely by echocardiogram. *Id*. Bloodwork, including a hepatic function panel, lipid panel, creatine kinase, and hemoglobin A1C, was ordered. Pet. Ex. 6 at 18; Pet. Ex. 7 at 12. Her creatine kinase and A1C were high and her HDL cholesterol was low. Pet. Ex. 4 at 17.

On September 13, 2013, Mrs. Halverson presented to her nephrologist and reported that she had passed out at home. Pet. Ex. 8 at 2. It was determined to be related to an adjustment of her water medication. *Id*.

On September 17, 2013, Mrs. Halverson presented to Dr. Sparagna for follow-up. Pet. Ex. 3 at 8. She reported occasional shortness of breath and was scheduled to have a defibrillator placed "next week." *Id*. at 11.

On September 30, 2013, Mrs. Halverson presented to Dr. Bullinga at Penn Presbyterian Medical Center for implantation of a permanent biventricular AICD. Pet. Ex. 6 at 24, 84; Pet. Ex. 7 at 100. She was noted to have had an exacerbation of congestive heart failure in May of 2013, a left ventricle ejection fraction of 25%, shortness of breath upon walking half a block, and NSVT into the 180s. *Id*. Her expected survival was greater than one year. Pet. Ex. 7 at 104. Blood work performed on October 22, 2013 showed low hemoglobin, hematocrit, MCH, MCHC, platelets, sodium, chloride, and eGFR, and high glucose, BUN, creatinine, BNP, and urine protein. Pet. Ex. 6 at 39-40; Pet. Ex. 7 at 163-64.

Petitioner testified that, after the implantation of the AICD, Mrs. Halverson's health improved. "She was doing a lot better. She had a lot more energy and…she was even thinking more positively about her health. She was more active…. She wanted to go out more and go out to restaurants…where she was mostly staying at home before. She didn't have the energy to do it." Tr. 42. She was also able to walk more. Tr. 42.

On November 8, 2013, Mrs. Halverson returned to Dr. Arluck for follow-up. Her pacemaker had been replaced with a biventricular AICD and she no longer had nocturnal dyspnea. Pet. Ex. 6 at 19; Pet. Ex. 7 at 14. She complained of shortness of breath when walking but attributed it to her unsteady gait and difficulty walking. *Id*. She did not climb steps. *Id*. She reported being given furosemide in the hospital, but got light headed, so she was only taking it when her weight was above 125 pounds. *Id*. She had severe chronic renal failure. *Id*. An electrocardiogram was performed; Mrs. Halverson was noted to have atrial and biventricular racing. Pet. Ex 4 at 4. She had not had any AICD discharges. Pet. Ex. 6 at 19.

On November 15, 2013, a cardiovascular disease risk profile was performed. Pet. Ex. 4 at 14-16. Her hemoglobin A1C and creatine kinase were high, and her HDL cholesterol was low. *Id*.

at 14-15; s*ee also* Pet. Ex. 3 at 5 (indicating that these lab results were discussed at a primary care appointment on January 9, 2014).

On December 12, 2013, Mrs. Halverson had an echocardiogram, which showed an estimated left ventricle ejection fraction of 45 to 55%. Pet. Ex. 4 at 2; Pet. Ex. 6 at 89; Pet. Ex. 7 at 96. Her left ventricular systolic function was most likely depressed but had markedly improved since the last study. *Id*. She had stage III abnormal diastolic function compatible with elevated left ventricular filling pressure. Pet. Ex. 4 at 2-3; Pet. Ex. 6 at 89-90; Pet. Ex. 7 at 96-97. She also had mild tricuspid regurgitation. Pet. Ex. 4 at 3; Pet. Ex. 6 at 90; Pet. Ex. 7 at 97.

Petitioner accompanied Mrs. Halverson to this appointment with Dr. Arluck on December 12, 2013. Tr. 19, 45. According to petitioner, Dr. Arluck "tweaked" the AICD and said that it needed a little adjustment, but that Mrs. Halverson was "doing fine." Tr. 45. Petitioner stated that Dr. Arluck "was one of the best pacemaker doctors in the country for that defibrillator pacemaker" and had written 11 books on the subject. Tr. 45-46. Petitioner testified that, at this time, Mrs. Halverson was upbeat and strong. Tr. 9, 46.

Petitioner recounted that on January 7 and 8, Mrs. Halverson "started to get a cough and started sneezing with congestion," which he described as a "slight cold." Tr. 8, 47. Petitioner did not recall having similar symptoms. Tr. 24. "I don't think so, but if I did, it wasn't very severe, to me." Tr. 24. Petitioner did not recall Mrs. Halverson being fatigued or having shortness of breath. Tr. 25-26. He recalled that they were talking about taking a trip. Tr. 26.

On January 9, 2014, Mrs. Halverson presented to Dr. Sparagna for a sick visit for nasal congestion, a loose but non-productive cough, "clogged" ears, and a scratchy throat for three days. Pet. Ex. 3 at 5. She also complained of numbness in her feet, fatigue, and occasional shortness of breath. *Id*. She reported difficulty hearing but no ear pain. *Id*. She walked with a cane for balance. *Id*. Upon exam, her heart rate was "regularly irregular" but she did not have difficulty breathing or shortness of breath. *Id*. She was noted to have hyperlipidemia, hypertension, type II diabetes, complete atrioventricular block, chronic ischemic heart disease, and an upper respiratory infection. *Id*. at 5, 7. Dr. Sparagna recommended Mucinex, saline nasal spray, and Tylenol or Advil. *Id*. at 7. She was administered Fluzone on that day. *Id*. at 2.

Petitioner recalled Mrs. Halverson receiving a flu shot during the appointment with Dr. Sparagna on January 9, 2014 and a prescription for her nasal congestion. Tr. 9, 10. Petitioner noted that Mrs. Halverson had diabetic neuropathy in her feet and "wasn't sure of herself walking up and down steps…or on uneven pavement, so she used the cane for balance" but "[s]he very rarely used the cane in the house." Tr. 25-26. He recalled after the doctor's appointment going together to Rite Aid to fill the prescription. Tr. 26. Mrs. Halverson did not have any difficulty walking around the drug store. Tr. 26.

According to the medical records, Mrs. Halverson received a tetanus-diphtheria vaccine in 2004; a diphtheria-tetanus-acellular pertussis vaccine on April 27, 2011; a pneumococcal vaccine on October 15, 2011; and a seasonal influenza preservative-free vaccine on October 9, 2012, without event. Pet. Ex. 3 at 9. January 9, 2014 was the first time Mrs. Halverson received Fluzone, the high-dose flu vaccine.

B. Mrs. Halverson's Health After Receiving the Fluzone

According to petitioner, Mrs. Halverson experienced "rapid degeneration" following the Fluzone vaccination. Tr. 11. About an hour after they ate dinner the night of the vaccination, Mrs. Halverson began vomiting and "continued to vomit every couple of hours." Tr. 11. She barely slept "because she kept throwing up, and she had a tremendous cough because of it…" Tr. 11.

Petitioner recalled Mrs. Halverson coughing throughout the night and into the next morning, January 10. Tr. 11. She had dry heaves. Tr. 28. She also started to lose her voice and her hearing. Tr. 12. She told him that her arms were numb and tingling. Tr. 12. She described it "like when your foot goes to sleep." Tr. 19. Tr. She had less than half of her normal energy. Tr. 12. She had to use a cane in the house when she normally only used it when she left the house. Tr. 12. He had to make sure that she could walk to the bathroom. Tr. 12-13.

According to petitioner, over the next several days, Mrs. Halverson continued to deteriorate. By Monday, January 13, she was "sitting there in a zombie-like state on the couch." Tr. 14, 18. She asked petitioner to lower a window shade that was about two feet away from the couch, where she was sitting. Tr. 14. Petitioner told her that if she could not lower the window shade in ten minutes, he would call an ambulance to take her to the hospital. Tr. 14. It took her the full ten minutes to stand up from the chair and lower the shade. Tr. 14-15. Petitioner asked her to go to the hospital or the doctor, but she resisted. Tr. 15. Finally, around 7:00 pm that night, she agreed that he could take her to the hospital. Tr. 15. She needed to go to the bathroom, but she could not walk, so petitioner carried her to the bathroom. Tr. 15-16. While she was in the bathroom, petitioner called Mrs. Halverson's sister, Linda, to ask her advice. Linda agreed that Mrs. Halverson needed to go to the hospital. Tr. 16. Petitioner recalled that, while he was on the phone, his wife called to him and then collapsed. He called 911. He was a volunteer fireman and trained in CPR, so he began performing CPR on Mrs. Halverson. The paramedics arrived and performed CPR and "shocked" her. Tr. 16; Pet. Ex. 9 at 20-21. According to petitioner, the paramedics were there for over an hour. Tr. 16. "[T]hey said they didn't revive her…but they cannot (sic) pronounce her dead, so they took her to the hospital." Tr. 16.

Mrs. Halverson arrived at Shore Medical Center in cardiorespiratory arrest. Pet. Ex. 9 at 16. Petitioner reported to hospital personnel that Mrs. Halverson had been ill for the "past few days" with an upper respiratory infection, malaise, weakness, decreased intake, cough, shortness of breath, nausea, vomiting, "retching," and congestion; she had an internal defibrillator. *Id*. at 16-17. She had "finally" agreed to go to the hospital and went to change her clothes first. *Id*. He called 911 and found her in the bathroom slumped over on the toilet. *Id*. He laid her on the floor and started CPR. *Id*. He reported that she had complained of shortness of breath before she collapsed. *Id*.

The hospital notes show that BLS (Basic Life Support) arrived and shocked Mrs. Halverson twice with an AED (automated external defibrillator), then medics arrived and shocked her an additional two times, while CPR continued with attempted failed intubation. Pet. Ex. 9 at 16. BVM (bag valve mask) was used to oxygenate. *Id*. During transport, she was shocked twice by medics and given IV epinephrine. *Id*. Upon arrival at the hospital, Mrs. Halverson had pacer spikes without a pulse; pacer spikes ceased with magnet placement. *Id*. Mrs. Halverson was intubated. *Id*. There

was no response to medical therapy. *Id*. at 17. Mrs. Halverson was shocked multiple times in the emergency room without success. *Id.* She was pronounced deceased at 11:14 pm. *Id*.

The immediate cause of death was cardiac arrest due to ischemic heart disease. Pet. Ex. 2 at 1. Other significant conditions contributing to death were diabetes myelitis, hyperlipidemia, arrhythmia and hypertension. *Id*. An autopsy was not performed. *Id*.

A note by Dr. Sparagna dated January 14, 2014, stated that he spoke with petitioner, who informed him that Mrs. Halverson had been ill and unable to breathe well for a few hours "yesterday." Pet. Ex. 4 at 62. Dr. Sparagna noted that petitioner told him, "Her defibrillator warning system did not go off. She suddenly fell to the floor, dead." *Id*.

At hearing, petitioner recalled that, after Mrs. Halverson's death, Dr. Sparagna called him and asked what happened. Tr. 40. Petitioner testified that he did not tell Dr. Sparagna that Mrs. Halverson's defibrillator warning system did not go off or make any statements about Mrs. Halverson's pacemaker and did not know whether or not her pacemaker fired. Tr. 17, 40-41. Petitioner stated that he did not know how the AICD worked and he would not know what it would look like if it did not go off. Tr. 41. He testified that he never saw the AICD "shock" Mrs. Halverson. Tr. 34.

IV. The Experts

A. Petitioner's Experts

1. Robert Stark, M.D.

Dr. Stark received his M.D. from Harvard Medical School, where he graduated with honors. Pet. Ex. 21 at 1. While at Harvard, he carried out a four-year research project in the Genetics Unit which focused on metabolic disorders and mutations in human cells in culture. Pet. Ex. 20 at 2. He then served as a clinical associate, a cardiology fellow, and the chief resident at the National Heart, Lung, and Blood Institute at the National Institutes of Health ("NIH"). Pet. Ex. 21 at 1. At the NIH, Dr. Stark carried out parallel biochemical and cellular studies investigating cholesterol metabolism and biochemical risk factors for heart attack. Pet. Ex. 20 at 2. He is board certified in internal medicine and cardiovascular disease. Pet. Ex. 21 at 2. Dr. Stark was a clinical cardiologist and internist at Greenwich Hospital, where he chaired the Cardiopulmonary Resuscitation Committee. *Id*. at 3; Pet. Ex. 20 at 2. He currently teaches preventive cardiology at the New York Medical College; he estimated that he spends five to ten percent of his time teaching. Tr. 76. He also has a private clinical practice. Tr. 104.

2. Gourang Patel, Pharm.D

Dr. Patel is a clinical pharmacist in the areas of pharmacy and pharmacology/toxicology at RUSH University Medical Center (RUSH), where he also has teaching appointments in several departments, including Pharmacy, Pharmacology, Anesthesiology, and Pulmonary and Critical Medicine. Pet. Ex. 22 at 1. He works with a clinical care team which includes the attending physician, resident, intern, and nurse to put together the patient's drug therapy plan, focusing on

maximizing benefits to the patient and minimizing side effects. Tr. 64. Dr. Patel is familiar with flu vaccine preparations and the pharmacology/toxicology of the flu vaccine, including its effect on the cardiovascular system and subsequent sequelae. Pet. Ex. 22 at 1.

B. Respondent's Experts

1. Joseph Murphy, M.D.

Dr. Joseph Murphy received his medical degree from University College Cork in Ireland. Resp. Ex. B at 2. He completed a year-long research fellowship in cellular cardiology at Harvard Medical School, followed by additional fellowships in clinical cardiology and invasive cardiology at the Mayo Clinic. *Id*. Dr. Murphy has been in full-time clinical practice as an attending cardiologist at the Mayo Clinic since 1990. *Id*.; Tr. 146. He is board certified in internal medicine, cardiology, transplant cardiology, and advanced heart failure. Resp. Ex. B at 3; Tr. 146. Dr. Murphy's interests include critical care cardiology, pulmonary hypertension, and valvular heart disease. Resp. Ex. A at 2. Dr. Murphy estimated that 50 percent of his patients have advanced heart failure due to a variety of conditions. Tr. 148. He sends two or three patients per week to have AICDs placed. Tr. 148. He published an article on vaccine-associated myocarditis after treating Army members who had cardiac complications following receipt of a smallpox vaccine. Tr. 150-51.

2. Noel Rose, M.D., Ph.D.

Dr. Rose is a Professor Emeritus at Johns Hopkins University, with appointments in the departments of Pathology and Medicine, Microbiology and Immunology, and Environmental Health Sciences. Resp. Ex. D at 1; Resp. Ex. E at 1. He was the founding director of the Johns Hopkins Center for Autoimmune Disease Research and is the former director of the Division of Immunology in the Department of Pathology and former Chairman in the Department of Immunology and Infectious Diseases. *Id*. He is presently a senior lecturer in the Department of Pathology at Brigham and Women's Hospital. *Id*. Dr. Rose is board certified in clinical pathology, microbiology, and laboratory immunology. Tr. 237-38. His practice does not involve treating patients. Tr. 243. Dr. Rose's published works include the Manual of Clinical Immunology, a textbook of immunology applied to medical practice. Tr. 234. He is also a co-editor of the textbook The Autoimmune Disease. Tr. 234-35.

V. Legal Framework

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec'y of Health & Human Servs*., 618

F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *See Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[14]

To prove causation for an "off-Table" injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id*. at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. Under the first *Althen* prong, petitioner must provide a "reputable medical theory" demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id*. at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Secretary of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). Even if the vaccination can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs*., 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id*. at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury,"

[14] The Vaccine Act also requires petitioners to show by preponderant evidence the vaccinee suffered from the "residual effects or complications" of the alleged vaccine-related injury for more than six months, died from the alleged vaccine-related injury, or required inpatient hospitalization and surgical intervention as a result of the alleged vaccine-related injury. § 11(c)(1)(D). It is undisputed that this requirement is satisfied in this case.

Paluck v. Sec'y of Health & Human Servs., 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375).

The third *Althen* prong requires that petitioner establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id*. However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id*.; *see also Locane v. Sec'y of Health & Human Servs*., 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

A petitioner may also be eligible for compensation if the vaccinee had a preexisting condition which was significantly aggravated by a vaccine. *See* § 11(c)(1)(C). In considering a significant aggravation claim for an on-Table injury, the Federal Circuit placed the most significance on whether petitioner's symptoms began within the time period proscribed. *Whitecotton v. Sec'y of Health & Human Servs*., 81 F.3d 1099, 1107 (Fed. Cir. 1996) ("Instead of asking whether the person's symptoms would have occurred absent the vaccine, our test hoves close to the statutory mandate, and relieves a petitioner of the burden of proving causation if she can show that the first symptom or manifestation of the significant aggravation of her condition occurred within the table time period provided in the statute.").

For a significant aggravation claim for an off-Table injury, the petitioner's burden is expanded to six elements, requiring petitioner to show, by preponderant evidence, proof of

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving ex rel. Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). The fourth, fifth, and sixth factors are derived from *Althen* prongs one, two, and three, respectively. *Id*. The Federal Circuit has agreed with this approach. *See W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) ("We hold that the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims.")

However, the third *Loving* factor, determining whether the person suffered a "significant aggravation" of his or her condition, leads to the question of what constitutes a significant

aggravation. Based on the legislative history and the language of the statute, it appears that Congress intended for a "significant aggravation" of a condition to present rather dramatically. *See* H.R. Rep. 908, 99th Cong.2d Sess. 1, reprinted in 1986 USCCAN 6287, 6356 ("This [significant aggravation] provision does not include compensation for conditions which might legitimately be described as preexisting (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), *but is meant to encompass serious deterioration* (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis" (emphasis added)); *see also* 42 U.S.C. § 300aa-33(4) ("The term "significant aggravation" means any change for the worse in a preexisting condition which results in *markedly greater* disability, pain, or illness accompanied by *substantial deterioration* of health" (emphases added)).

Once a petitioner has established that his or her condition worsened post-vaccination, the special master must determine "whether the change for the worse in [petitioner's] clinical presentation was aggravation or a natural progression" of the preexisting condition. *Hennessey*, 2009 WL 1709053 at *42. In doing so, special masters have relied on evidence supporting the "typical" clinical course of the petitioner's condition. *See, e.g., Locane*, 685 F. 3d at 1381-82 (Special master's determination that petitioner's Crohn's disease was not significantly aggravated by her hepatitis B vaccinations where her disease flare-ups after her first and third vaccinations were typical of frequent flares in adolescents' expected course of Crohn's disease was reasonable); *Faoro v. Sec'y of Health & Human Servs*., No. 10-704V, 2016 WL 675491, at *27 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. for review denied*, 128 Fed. Cl. 61 (Fed. Cl. Apr. 11, 2016) (finding that "the vaccinations would not have changed her clinical course and thus, the vaccinations did not significantly aggravate her preexisting condition").

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are presumed to be accurate and "complete" such that they present all relevant information on a patient's health problems. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). In making contemporaneous reports, "accuracy has an extra premium" given that the "proper treatment hang[s] in the balance." *Id.* Contemporaneous medical records that are clear, consistent, and complete warrant substantial weight "as trustworthy evidence." *Id*. Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948). But petitioners can support their claim with oral testimony if it is credible and consistent with the medical records. *See, e.g., Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). In short, "the record as a whole" must be considered. § 13(a).

Furthermore, establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence.

"In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Finally, although this decision discusses much but not all of the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Discussion

Because petitioner does not allege an injury listed on the Vaccine Injury Table, his claim is classified as "off-Table." As noted above, for petitioner to prevail on an "off-Table" claim, he must show by preponderant evidence that the influenza vaccine at issue either caused Mrs. Halverson's cardiac arrest and subsequent death or significantly aggravated her preexisting ischemic heart disease. *Capizzano*, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that Mrs. Halverson's injuries and death were caused by factors unrelated to the vaccination. *Deribeaux*, 717 F.3d at 1367.

Due to the requirement to prove causation, one special master has recommended evaluating "the last three *Loving* factors first." *Hennessey v. Sec'y of Health & Human Servs.*, No. 01–190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009), *motion for review denied*, 41 Fed. Cl. 126 (2010).

A. *Althen* Prong 1/Loving Factor 4: Reputable Medical Theory

Petitioner's experts opined that Fluzone can cause a systemic inflammatory response, sometimes referred to as "systemic inflammatory response syndrome," or "SIRS." Dr. Stark explained that SIRS can cause a variety of cardiac complications, including sudden cardiac death and myocardial infarction. *See* Pet. Ex. 18 at 3.

1. Fluzone can cause a systemic inflammatory response

According to Dr. Stark, Fluzone[15] is an immunologically enhanced alternative to the conventional flu vaccine and confers greater protection against infection than the conventional vaccine. Pet. Ex. 18 at 1. He emphasized that Fluzone is "a highly immunogenic flu vaccine that triggers an enhanced antibody response and systemic inflammation." Pet. Ex. 19 at 3. "This vaccine is deliberately enhanced to form more antibodies, [and] more immune response . . .". Tr. 91. As a result, Fluzone induces a greater immune response than the regular flu vaccine. Pet. Ex. 18 at 4. Dr. Patel added that Fluzone contains three strains of three different types of viruses. Tr. 52. Both Dr. Stark and Dr. Patel added that Fluzone contains four times more antigen than the regular seasonal flu vaccine. Tr. 53; Pet. Ex. 18 at 4. According to Dr. Patel, if a person who had symptoms of an upper respiratory infection ("URI") received Fluzone, the effects of the vaccine would be magnified, because the immune system would already be activated by the URI. Tr. 58.

Respondent's experts agreed that Fluzone is a powerful vaccine. Dr. Murphy stated that the influenza A vaccine "excites a strong immune reaction as it is designed to do, with spillover effects on many biological systems and functions that can be clearly demonstrated on laboratory testing." Resp. Ex. A at 23. Dr. Rose explained that flu vaccines contain a purified protein called hemagglutinin, which causes agglutination, or clumping, of red blood cells. Tr. 255; Resp. Ex. D at 2. Fluzone contains four times the usual amount of hemagglutinin found in the standard seasonal flu vaccine. Resp. Ex. D at 2; Tr. 257. Dr. Rose noted that, in a study of 30,000 patients who randomly receive either the high-dose or standard-dose flu vaccine, "[a]ntibody levels to the influenza hemagglutinin were significantly higher in the high dose group." Resp. Ex. D at 3; Resp. Ex. D, Tab 3.[16]

Petitioner's experts opined that patients are more likely to develop adverse events in response to Fluzone than the standard-dose flu vaccine. Dr. Stark stated that the CDC has reported a higher rate of adverse events in Fluzone recipients when compared with patients receiving the conventional flu vaccine. Pet. Ex. 17 at 2; Pet. Ex. 18 at 4.[17] According to Dr. Stark, cardiac disorders and infections are the most frequent types of serious adverse events reported. Pet. Ex. 18 at 4. Dr. Patel noted that a higher rate of generalized weakness is reported by patients who receive Fluzone than patients who receive a regular flu vaccination. Pet. Ex. 22 at 2.

Both of petitioner's experts cited statistics on adverse events following Fluzone. Dr. Stark noted that about 30% of patients develop an immune/hypersensitivity reaction at the injection site within three days of immunization, while 8 to 10% of patients develop systemic reactions,

[15] Dr. Murphy explained that elderly patients have diminished immune responses when compared to younger patients. Resp. Ex. O at 3. Fluzone, a more potent vaccine, is given to combat this effect. *Id*.

[16] Carlos A. Diaz Granados, et al., *Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults*, 371 N. ENGL. J. MED. 7: 635-45 (2014), filed as "Pet. Ex. 11," "Pet. Ex. 30," and "Resp. Ex. D, Tab 3."

[17] As a reference for this statement, Dr. Stark cited "Centers for Disease Control "Fluzone-High Dose Influenza Vaccine" 8/19/15." *See* Pet. Ex. 18 at 5. This reference was not filed as an exhibit.

including myalgias, malaise, fever, and headache in response to the vaccine. Pet. Ex. 18 at 2. Dr. Stark also referenced literature showing that the flu vaccine can cause the production of inflammatory substances measurable in the blood stream, such as cytokines, including tumor necrosis factor ("TNF"), and migration-inhibitory factor ("MIF"). Pet. Ex. 20 at 2; Resp. Ex. D, Tab 13.[18] "It is well recognized that inflammatory products lead to increased platelet aggregation and blood clotting." Pet. Ex. 20 at 2. According to Dr. Patel, up to 30% of patients develop an immune phenomenon which can trigger a host of responses, including increased coagulation and systemic/local vessel spasm, collectively referred to as systemic inflammatory response syndrome ("SIRS"). Pet. Ex. 22 at 2. According to Dr. Patel, SIRS presents as "a whole body malaise, deterioration and fatigue…" and usually has an identifiable trigger. Tr. 72.

2. A systemic inflammatory response affects cardiac function

Dr. Stark explained that the systemic inflammatory response triggered by Fluzone can cause an increase in platelet aggregation, which can lead to coronary obstruction or heart attack and result in cardiac arrest. The inflammatory response can also increase cardiac autonomic function, which can lead to cardiac arrythmias.

Drs. Stark and Patel opined that Fluzone can trigger a systemic inflammatory response which increases platelet aggregation, thereby increasing blood clotting. *See* Pet. Ex. 18 at 2; Pet. Ex. 19 at 3; Pet. Ex. 22 at 4. Dr. Patel added that a systemic inflammatory reaction will also cause increased blood pressure and heart rate; the increased clotting and systemic and local vessel spasms caused by SIRS can lead to a significant imbalance in oxygen demand and supply to the heart. Pet. Ex. 22 at 2, 4. The lack of oxygen ultimately leads to myocardial ischemia and myocardial infarction, which can trigger cardiac arrest. *Id*.

According to Dr. Stark, inflammation, allergic reaction, or infection can cause white blood cells to generate substances which cause platelets to become stickier; the platelets become more likely to clump and cause blockages. Tr. 90. Platelet activation has a prothrombotic effect that increases the risk of coronary obstruction and myocardial infarction in patients with underlying coronary artery disease. Pet. Ex. 18 at 2-3. A systemic inflammatory response can also trigger cardiac autonomic dysfunction by increasing heart rate and elevating contractility. *Id*. at 2; Pet. Ex. 19 at 2. Cardiac autonomic dysfunction predisposes individuals to potentially fatal ventricular arrhythmias, particularly if the coronary arteries are already compromised. Pet. Ex. 18 at 2-3. Dr. Stark explained that an increased immune response can affect the balance between two nerves that regulate the heartbeat. Tr. 91-92. "The vagus nerve makes the heart beat slower, and relax a little bit, [and] the sympathetic nerve makes the heart beat faster and harder." Tr. 92. "When you get an immunization, and you induce an immune response, the balance between vagal stimuli slowing the heart and sympathetic stimuli speeding up the heart, that balance is thrown off and that's not good for you if your heart is already impaired in any way." Tr. 92.

To support his theory, Dr. Stark offered the Lanza paper, which found, "Together with an inflammatory reaction, influenza A vaccine induced platelet activation and sympathovagal imbalance…suggesting a pathophysiological link between inflammation and cardiac autonomic

[18] Lisa M. Christian et al., *Proinflammatory cytokine responses correspond with subjective side effects after influenza virus vaccination,* 33 VACCINE 3360-66 (2015), filed as "Resp. Ex. D, Tab 13."

regulation. The vaccine-related platelet activation and cardiac autonomic dysfunction may transiently increase the risk of cardiovascular events." Pet. Ex. 10 at 1; Pet. Ex. 28 at 1.[19] This was a smaller study and the authors did not conclude that there is a direct causal relationship between inflammatory stimulus and platelet activation. However, the study did find a correlation between influenza vaccination and cardiac autonomic imbalance which warranted further investigation. Similarly, a study by Willerson and Ridker found that "[e]pidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events." Pet. Ex. 33 at 1.[20]

Dr. Patel explained that platelets have a role in the immune system, engulfing antigens in the body, whether the antigens are bacteria or vaccines. Tr. 58. When a vaccine is introduced to the body, the platelets aggregate around the antigen, causing clumping. Tr. 58. Dr. Patel offered four studies analyzing adverse cardiac events following flu vaccine. A 2012 study by Moro found that, between July 2010 and December 2010, the Vaccine Adverse Event Reporting System ("VAERS") received 606 reports of people 65 years and older who experienced adverse events after receiving a high-dose influenza vaccine. Pet. Ex. 12 at 1.[21] Of 51 reports considered serious events, nine (18%) were cardiac events; all nine patients had preexisting cardiac conditions. *Id*. at 3. In contrast, cardiac events were only 5% of serious events occurring after a standard-dose influenza vaccine. *Id*. The authors concluded that adverse event reporting for cardiac events may be "unexpectedly higher" after receipt of the high-dose flu vaccine than the standard-dose flu vaccine. *Id*. at 5.

In 2013, Moro issued another study of patients who received an intradermal flu vaccine; three out of the nine serious events were cardiac events. *See* Pet. Ex. 14 at 2-3.[22] The only fatal event was an 88-year-old woman who had sudden cardiac death 16 days after vaccination. *Id*. at 3.

Additionally, Haber studied adults 18 to 49 years old who received the standard-dose trivalent flu vaccine between 2005 and 2013; of 107 serious events, 14 patients (13.6%) experienced cardiac adverse events, including myocardial infarction and arrhythmias. Pet. Ex. 13

[19] Gaetano A. Lanza et al., *Inflammation-related effects of adjuvant influenza A vaccination on platelet activation and cardiac autonomic function,* 269 J. INTERN. MED. 118-25 (2011), filed as "Pet. Ex. 10" and "Pet. Ex. 28."

[20] James T. Willerson and Paul M. Ridker, *Inflammation as a Cardiovascular Risk Factor*, 109 CIRCULATION 21: 2-10 (2004), filed as "Pet. Ex. 33."

[21] Pedro L. Moro et al., *Postlicensure Safety Surveillance for High-Dose Trivalent Inactivated Influenza Vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010,* 54 CLIN. INFECT. DIS. 11: 1608-14 (2012), filed as "Pet. Ex. 12," "Pet. Ex. 25," and "Pet. Ex. 29."

[22] Pedro L. Moro et al., *Adverse events after Fluzone Intradermal vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), 2011-2013*, 31 VACCINE 4984-87 (2013), filed as "Pet. Ex. 14."

at 1, 3.[23] In six of the 14 adverse events, smallpox vaccine was given concurrently with the flu vaccine. *Id*. at 4. Another Haber study which examined adverse events following the quadrivalent flu vaccine found nine serious events, two of which were cardiovascular and included myocardial infarction. Pet. Ex. 15 at 3.

Dr. Rose criticized Dr. Patel's reliance on the Moro and Haber studies due to their use of data from VAERS. Drs. Stark, Patel, and Rose agreed that VAERS is a passive reporting system and that VAERS data cannot be used to establish a causal relationship between a vaccine and a certain adverse event. Pet. Ex. 20 at 1; Tr. 68, 287.

Ultimately, however, Dr. Rose seemed to agree that systemic inflammation can affect cardiac autonomic function. *See* Resp. Ex. V at 3 ("A recent review…discusses our current understanding of the role of inflammation in the pathogenesis of atrial fibrillation, a common manifestation of systemic inflammation on the heart.") He also cited several studies that confirmed an association between inflammation and atrial fibrillation. *Id*.; *see* Resp. Ex. V, Tab 1;[24] Resp. Ex. V, Tab 2;[25] Resp. Ex. V, Tab 3;[26] Resp. Ex. V, Tab 4;[27] Resp. Ex. V, Tab 5.[28] Still, he cautioned that "[t]here is no data to suggest that inflammation is the sole or even major risk factor for atrial fibrillation." Resp. Ex. V at 3.

3. Respondent submits that literature does not support petitioner's theory

Dr. Rose and Dr. Murphy submitted a variety of articles in support of their assertions that (1) Fluzone does not cause SIRS; (2) Fluzone does not cause adverse cardiovascular events; and (3) Fluzone protects against adverse cardiovascular events.

According to Dr. Rose, "A clinical definition of SIRS is still under discussion but still requires a broad array of multi-organ dysfunctions." Resp. Ex. D at 6, citing Irene Cortes-Puch and Christiane S. Hartog, *Change Is Not Necessarily Progress: Revision of the Sepsis Definition*

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[23] Penina Haber et al., *Post-licensure surveillance of trivalent live attenuated influenza vaccine in adults, United States, Vaccine Adverse Event Reporting System (VAERS), July 2005-June 2013*, 32 VACCINE 6499-6504 (2014), filed as "Pet. Ex. 13."

[24] Yu-Feng Hu et al., *Inflammation and the pathogenesis of atrial fibrillation*, 12 NAT. REV. CARDIOL. 230-243 (2015), filed as "Resp. Ex. V, Tab 1."

[25] Anna Borowiec et al., *Prospective assessment of cytokine IL-15 activity in patients with refractory atrial fibrillation episodes*, 74 CYTOKINE 1: 164-70 (2015), filed as "Resp. Ex. V, Tab 2."

[26] Renate B. Schnabel et al., *Relations of Biomarkers of Distinct Pathophysiological Pathways and Atrial Fibrillation Incidence in the Community*, 121 CIRCULATION 2: 200-07 (2010), filed as "Resp. Ex. V, Tab 3."

[27] Dwayne S.G. Conway et al., *Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation*, 148 AM. HEART J 3: 462-66 (2004), filed as "Resp. Ex. V, Tab 4."

[28] David Conen et al., *A multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women*, 31 EUR. HEART J. 1730-36 (2010), filed as "Resp. Ex. V, Tab 5."

Should Be Based on New Scientific Insights, 194 AM. J. RESPIR. CRIT. CARE MED. 16-18 (2016).[29] However, he did note that the clinical symptoms associated with SIRS include fever, malaise, change in heart rate, headache, inordinate fatigue and exhaustion, muscle aches and pains, and chills. Tr. 263.

Although Dr. Rose agreed that the Sanofi-Pasteur[30] literature states that the most common systemic adverse events associated with Fluzone were myalgia, malaise, and headache, he did not believe that Fluzone was capable of causing a systemic inflammatory response. Tr. 297. "A stimulus such as a vaccine comprising purified peptides with no added adjuvant is highly unlikely to give rise to an uncontrolled, continuing inflammatory response unless the host has some genetic abnormality or previous experience that would prepare her for such a pathologic reaction." Resp. Ex. D at 6. He stated that, regardless of whether one uses the term "out of control inflammatory syndrome or "enhanced inflammatory response," there is no objective evidence that Fluzone induces greater systemic inflammation than the standard flu vaccine. Resp. Ex. V at 2. "Although there is evidence from clinical trials that the high dose vaccine induces higher levels of circulating antibody. (sic) There are no published investigations of humans documenting and quantitating an enhanced, generalized inflammatory response." *Id*.

Dr. Rose submitted that the best support for petitioner's theory that Fluzone can cause SIRS would be serial studies of blood samples taken periodically after vaccination; however, these studies are rarely performed in humans. Resp. Ex. D at 5; *see also* Resp. Ex. D, Tab 13; Resp. Ex. D, Tab 14;[31] Resp. Ex. D, Tab 15;[32] Resp. Ex. D, Tab 16.[33] Dr. Rose referenced several studies which have performed these tests, noting that the inconsistent results between studies illustrates the technical and logistical difficulty in assessing cytokine levels in human blood. Resp. Ex. D at 5.

Dr. Rose opined that a causal connection between Fluzone and an adverse cardiovascular event would require a "statistical association between high dose Fluzone and the initiation or enhancement of cardiovascular disease…" Resp. Ex. D at 6. The literature does not support such an association. He offered several studies in support of this opinion. A 2014 study funded by Sanofi-Pasteur evaluated the effectiveness of a high-dose trivalent influenza vaccine in adults 65

[29] This article was not filed into the record.

[30] Sanofi-Pasteur is the manufacturer of Fluzone. *372 Fluzone High-Dose*, SANOFI-PASTEUR (Revised July 2017), filed as "Pet. Ex. 31.")

[31] Helder I. Nakaya et al., *Systems biology of vaccination for seasonal influenza in humans*, 12 NAT IMMUNOL 8: 786-96 (2011), filed as "Resp. Ex. D, Tab 14."

[32] Petru Liuba et al., *Residual adverse changes in arterial endothelial function and LDL oxidation after a mild systemic inflammation induced by influenza vaccination*, 39 ANN. MED. 5: 392-99 (2007), filed as "Resp. Ex. D, Tab 15."

[33] Michael Y. Tsai et al., *Effect of influenza vaccine on markers of inflammation and lipid profile*, 145 J. LAB. CLIN. MED. 6: 323-27 (2005), filed as "Resp. Ex. D, Tab 16."

years of age and older. Resp. Ex. D, Tab 3 at 1-2.[34] It found that the high-dose trivalent flu vaccine "induced significantly higher antibody responses" than the standard-dose flu vaccine. *Id*. at 1. However, the study found that the number of deaths following the high-dose vaccine and standard-dose vaccine was "essentially identical," and the deaths were classified as unrelated to the vaccine. Resp. Ex. D at 3; *see also* Resp. Ex. D, Tab 3 at 6 (stating that 83 of 15,990 participants in the high-dose group died, as did 84 of 15,993 participants in the standard-dose group).

Dr. Rose also referred to several studies analyzing data from VAERS. Another Moro study analyzed adverse events following the trivalent standard-dose flu vaccine from 2013 to 2015; of 309 reported adverse events, only five were cardiac events. Resp. Ex. D, Tab 6 at 3.[35] The authors of the study "did not identify any concerning pattern" of adverse events. *Id*. at 1. Similarly, a Haber study also analyzed adverse events from 2013 to 2015 but examined the quadrivalent standard-dose flu vaccine. Resp. Ex. D, Tab 7 at 1.[36] Haber found that, of 127 serious reports of adverse events, there were 12 deaths reported following this flu vaccine from a variety of causes, including ventricular tachycardia leading to cardiac arrest/cardiogenic shock, dilated cardiomyopathy, inferior wall myocardial infarction, and heart failure. *Id*. at 4. There were an additional four reports of cardiac adverse events. *Id*. Nonetheless, Haber "did not identify any safety concerns" for the flu vaccine. *Id*. at 5.

Additionally, Dr. Rose offered studies which conducted active surveillance, rather than passive surveillance, of potential adverse effects of the flu vaccine. A Sanofi-Pasteur funded study examining the effects of Fluzone administered to adults 65 years of age and older showed that 116 out of 319 recipients experienced systemic effects of the vaccine, but only 16 recipients experienced a serious adverse event. Resp. Ex. D, Resp. at 7.[37] According to Dr. Rose, the serious adverse events consisted of vomiting or severe cough, and none suggested cardiac disease. Resp. Ex. D at 4. Dr Rose also cited to the 2012 IOM report, which concluded, "The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and myocardial infarction." Resp. Ex. D, Tab 5 at 5.[38] The IOM report recognized that, "[w]hile rare, influenza infection has been associated with myocardial infarction…" it ultimately assessed the evidence of such an association as "lacking." *Id*. at 4. The IOM committee placed great weight on a 2004 study

[34] *See supra* n.16.

[35] Pedro L. Moro et al., *Surveillance of adverse events after the first trivalent inactivated influenza vaccine produced in mammalian cell culture (Flucelvax®) reported to the Vaccine Adverse Event Reporting System (VAERS), United States, 2013-2015*, 33 VACCINE 6684-88 (2015), filed as "Resp. Ex. D, Tab 6."

[36] Penina Haber et al., *Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013-May 31, 2015*, 34 VACCINE 2507-12 (2016), filed as "Resp. Ex. D, Tab 7."

[37] Peter Tsang et al., *Immunogenicity and safety of Fluzone intradermal and high-dose influenza vaccines in older adults ≥65 years of age: A randomized, controlled, phase II trial*, 32 VACCINE 2507-17 (2014), filed as "Resp. Ex. D, Tab 8."

[38] Kathleen Stratton et al., eds., ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY, pp. 387-89 (2012) ["2012 IOM Report"], filed as "Resp. Ex. D, Tab 5."

by Smeeth, which was submitted by respondent's experts as Resp. Ex. M.[39] Smeeth reported that there was no increased risk of myocardial infarction within one month following influenza vaccination. Resp. Ex. D, Tab 5 at 4; *see also* Resp. Ex. M at 1. The IOM committee placed "a moderate degree of confidence in the epidemiologic evidence based on" the Smeeth study. *Id*. Neither the Smeeth study nor the IOM report addressed Fluzone.

Dr. Stark agreed with Dr. Rose there is no epidemiologic evidence suggesting that Fluzone has a poorer safety record or increased adverse reactions in recipients compared to the standard-dose flu vaccine but suggested that this was because no one has looked for such a correlation. Pet. Ex. 17 at 1.

Both of respondent's experts opined that medical literature does not support the view that Fluzone can induce or aggravate existing cardiovascular disease. Resp. Ex. D at 4; Resp. Ex. O at 9. To the contrary, both Dr. Rose and Dr. Murphy submitted literature indicating that the flu vaccine protects recipients from adverse cardiovascular events. However, none of these studies administered Fluzone to a subject who was already ill.

As an example, Dr. Rose offered a study published by the Cochrane Library which evaluated "8 trials of influenza vaccination compared with placebo or no vaccination in 12,029 individuals." Resp. Ex. D at 4, referencing Resp. Ex. D, Tab 10.[40] According to Dr. Rose, this study "found that cardiovascular mortality was significantly reduced by influenza vaccination as were cardiovascular events." *Id*. Dr. Rose explained that instances of acute myocardial infarction increase during flu season; some studies show that the risk of myocardial infarction or stroke is more than four times higher after a respiratory tract infection, with the highest risk within three days. *Id*.

Another paper submitted by Dr. Rose analyzed case control studies on flu vaccine, flu infection, and acute myocardial infarction, and found that flu infection significantly raised the risk of disability and death in patients with ischemic heart disease. Resp. Ex. D at 5, referencing Resp. Ex. D, Tab 12.[41] The article suggested that flu infection can lead to myocardial infarction "via acute coronary occlusion through thrombosis of a pre-existing, subcritical atherosclerotic plaque... Infection causes tachycardia, hypoxia, release of inflammatory cytokines and a thrombophilic state," any of which can contribute to a myocardial infarction. Resp. Ex. D, Tab 12 at 1.

The Udell article offered by Dr. Rose reported that a study of adults over 65 years old who received the high-dose flu vaccine were 24% less likely to develop the flu and also had a "reduced risk of pneumonia, all-cause hospitalization, and cardiopulmonary events with no increase in

[39] Liam Smeeth et al., *Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination*, 351 N. ENGL. J. MED. 25: 2611-18 (2004), filed as "Resp. Ex. M."

[40] Christine Clar et al., *Influenza vaccines for preventing cardiovascular disease (Review)*, 5 COCHRANE DATABASE SYST. REV. 1-55 (2015), filed as "Resp. Ex. D, Tab 10."

[41] Michelle Barnes et al., *Acute myocardial infarction and influenza: a meta-analysis of case-control studies*, 101 HEART 1738-47 (2015), filed as "Resp. Ex. D, Tab 12."

serious adverse events compared with standard-dose vaccine." Resp. Ex. D, Tab 9 at 3.[42] Dr. Rose concluded, "In brief, there is no direct positive evidence for either an epidemiological association or a plausible mechanism to link Fluzone High Dose to the fatal heart failure in Mrs. Halverson." Resp. Ex. D at 7.

Dr. Murphy emphasized that the American Heart Association and American College of Cardiology ("AHA/ACC") recommends the flu vaccine for all cardiac patients. Tr. 160; Resp. Ex. A at 2, 7. He recommends that his own patients with advanced heart failure receive the flu vaccine. Tr. 160. He explained, "patients with heart disease are generally very fragile, and are at very high risk if they get the flu, that it will decompensate, get arrhythmias, get heart failure, and the overwhelming evidence is that they benefit significantly from it." Tr. 160-61. In Dr. Murphy's opinion, "there is no good evidence that the flu vaccine is harmful to [patients with heart failure]." Tr. 161.

Dr. Murphy stated that flu vaccine, like any vaccine, is intended to excite an immune response. Resp. Ex. O at 3. The elderly have diminished immune responses when compared to younger patients, so a more potent vaccine is given to combat this effect. *Id*. The overall consensus is that influenza vaccine is beneficial in the elderly when compared to the risk of actual influenza. *Id*. at 4. In a 2006 paper, the AHA/ACC recommended the flu vaccine as secondary prevention for patients with coronary and other atherosclerotic disease. Resp. Ex. A at 7; Resp. Ex. L.[43] Notably Dr. Stark pointed out that this recommendation was made three years before Fluzone was introduced, and therefore did not consider the potential consequences of a more potent vaccine. Pet. Ex. 19 at 2.

Dr. Murphy submitted several other articles to support his opinion that Fluzone protects against cardiac events. A 2003 paper from the New England Journal of Medicine found that flu vaccination was associated with a reduction in hospitalizations for heart disease, cerebrovascular disease, pneumonia, and influenza, which supports the benefits of flu vaccines for the elderly. Resp. Ex. A at 6; Resp. Ex. K.[44] The Naghavi study found that patients with coronary heart disease and a history of myocardial infarction who received the flu vaccine were 67% less likely to have a subsequent myocardial infarction. Resp. Ex. Q at 3.[45] Similarly, the Grau study found that patients with a history of stroke or transient ischemic attack who received the flu vaccine were less likely to have a subsequent stroke. Resp. Ex. R at 2-3, 6.[46] A fourth study found that, while "acute

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[42] Jacob A. Udell et al., *Does influenza vaccination influence cardiovascular complications?*, 13 EXPERT REV. CARDIOVASC. THER. 6: 593-96 (2015), filed as "Resp. Ex. D, Tab 9."

[43] *See supra* n.9.

[44] *See supra* n.8.

[45] Morteza Naghavi et al., *Association of Influenza Vaccination and Reduced Risk of Recurrent Myocardial Infarction*, 102 CIRCULATION 3039-45 (2000), filed as "Resp. Ex. Q."

[46] Armin J. Grau et al., *Influenza Vaccination Is Associated With a Reduced Risk of Stroke*, 36 STROKE 1501-06 (2005), filed as "Resp. Ex. R."

infections are associated with a transient increase in the risk of vascular events. . . influenza, tetanus, and pneumonia vaccinations do not produce a detectable increase in the risk of vascular events." Resp. Ex. M at 1.[47] None of the studies discussed by Dr. Murphy examined the effects of Fluzone on patients already suffering from an upper respiratory infection at the time of vaccination.

When asked about incidences of myocardial infarction after receipt of Fluzone as noted in the package insert,[48] Dr. Murphy agreed that there have been incidences of myocardial infarction after the administration of Fluzone but stated that these are "serendipitous events" which occur due to the high number of heart attacks that occur every year in the U.S. Tr. 162. He agreed that the relationship between Fluzone and myocardial infarction is "[n]ot necessarily causal, but it could be." Tr. 162.

4. *Althen* Prong 1/*Loving* Fact 4: Discussion

Dr. Stark and Dr. Patel opined that Fluzone, which contains four times more antigen than the regular flu vaccine, can cause a susceptible individual to develop a systemic inflammatory response. This response triggers platelet aggregation and increased blood clotting, which can cause myocardial infarction leading to cardiac arrest. They supported these opinions with medical literature. Dr. Stark offered the Lanza study finding that flu vaccine-related platelet activation and cardiac autonomic dysfunction can increase the risk of cardiovascular events. *See* Pet. Ex. 10 at 1. In turn, Dr. Patel submitted four studies showing that some patients had adverse cardiac events, including myocardial infarction and cardiac arrest, following receipt of a flu vaccine. *See* Pet. Ex. 12; Pet. Ex. 14; Pet. Ex. 13; Pet. Ex. 15.

Dr. Rose and Dr. Murphy offered a bevy of literature to support their position that Fluzone cannot induce or aggravate existing cardiovascular disease, but rather is protective against adverse cardiovascular events. Dr. Rose criticized the studies offered by Dr. Patel for using data from VAERS; however, Dr. Rose also cited to studies which relied on VAERS data to support his point that Fluzone does not cause adverse cardiac events.

Neither Dr. Rose nor Dr. Murphy pointed to any deficits in petitioner's theory. Conversely, Dr. Rose noted that a protein in the flu vaccine, hemagglutinin, increases clumping of red blood cells, and is four times higher in Fluzone than the regular flu vaccine. At hearing, he agreed that it was possible for incidences of myocardial infarction to be associated with Fluzone. Tr. 288-89. Despite these concessions, Dr. Rose maintained that there was no "statistical association," "epidemiological association," or "plausible mechanism" to provide a causal connection between Fluzone and adverse cardiac events.

However, "epidemiologic studies" are specifically not required in the Vaccine Program. Capizzano, 440 F.3d at 1325. The standard of proof is only "preponderance of evidence," in order "to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. To require petitioner to present a statistical association between a vaccine and a claimed injury would impermissibly raise the standard of

[47] *See supra* n.39.

[48] *See supra* n.30.

proof. And petitioner's experts have supported their theory with medical literature, thus providing the "indicia of reliability" to support their assertions. *Moberly*, 592 F.3d at 1324. Accordingly, I find that petitioner's experts have proffered a sound, reliable medical theory that Fluzone can cause a systemic inflammatory response and increase clotting of red blood cells.

Petitioner has satisfied *Althen* prong 1/*Loving* factor 4.

B. *Althen* Prong 2/Loving Factor 5: Logical Sequence of Cause and Effect

Dr. Stark testified that Mrs. Halverson developed a systemic inflammatory response, which caused platelets to form or cause a blockage in the coronary arteries. Tr. 101. This caused her to suffer an acute coronary event, a heart attack, resulting in cardiac arrest. Tr. 101. He explained that she suffered from a ventricular arrhythmia caused by a shortage of blood flow to her heart muscle because her coronary artery was blocked by platelets. Tr. 130.

According to Dr. Stark, there was both a pathological and temporal link to implicate the high dose flu vaccine in Mrs. Halverson's sudden death. Pet. Ex. 18 at 4. Fluzone induced systemic inflammation in Mrs. Halverson, which significantly increased her risk for arrhythmia, myocardial infarction, and sudden cardiac death, given her preexisting co-morbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, and congestive heart failure. Pet. Ex. 17 at 2; Pet. Ex. 19 at 2. He ultimately concluded that the Fluzone vaccine administered to Mrs. Halverson on January 9, 2014, caused a systemic inflammatory response which caused platelets to form, affecting blood flow to the heart. Tr. 101. This significantly aggravated her atrial fibrillation and secondarily worsened her underlying congestive heart failure and was a substantial factor in causing her ultimate cardiac arrest from which she could not be resuscitated. Pet. Ex. 18 at 1.

Dr. Patel similarly concluded that the Fluzone vaccine administered to Mrs. Halverson on January 9, 2014 was a significant contributing factor in causing an adverse cardiac event and her death on January 13, 2014. Pet. Ex. 22 at 3. "I believe it caused a hyper-response of the inflammation and immune system, which caused the platelets to aggregate together and cause subsequent cardiac events." Tr. 59. Dr. Patel agreed that Mrs. Halverson's URI symptoms indicated that she was already immunocompromised when she was administered the vaccine. Tr. 59.

1. Fluzone caused Mrs. Halverson to develop a systemic inflammatory response

According to Dr. Patel, following receipt of Fluzone, Mrs. Halverson developed symptoms consistent with the criteria for SIRS. Dr. Patel noted that she developed increased heart rate, increased respiratory rate or shortness of breath, and increased white cell count, adding that, if a person had an upper respiratory infection and then received Fluzone, the vaccine would have a magnified effect, "because the patient's immune system is already activated from an underlying condition." Tr. 58, 65-66. The effect would be synergistic. Tr. 58. Dr. Stark agreed that there was a synergistic effect between Fluzone and Mrs. Halverson's ongoing URI which worsened her cardiac condition. Tr. 101-02. He noted that she complained of shortness of breath post-vaccination and explained that an inflammatory response can affect breathing, causing shortness of breath. Tr. 134. It can also cause a person to feel weak. Tr. 134.

Dr. Patel could only speculate about Mrs. Halverson's symptoms, because there was no evidence in the record reflecting that Mrs. Halverson actually did experience increased heart rate, respiratory rate, and/or white cell count following her receipt of Fluzone. Tr. 65-66. Dr. Patel conceded that diagnosing patients is not within the boundaries of his pharmacist licensure, and he would defer to a medical doctor for diagnostic purposes. Tr. 67.

Petitioner reported to the paramedics and emergency room physicians that, in the days that followed her receipt of Fluzone, Mrs. Halverson grew weaker, had lethargy, malaise, and shortness of breath, and could not get up off of the couch. He also reported these symptoms to Dr. Sparagna after she passed. *See* Pet. Ex. 9 at 16-17; Pet. Ex. 4 at 62; Tr. 12-15.

Dr. Rose offered a Sanofi-Pasteur study showing recipients of the flu vaccine experiencing vomiting and severe cough. Resp. Ex. D, Tab 8 at 7.[49] Petitioner testified to Mrs. Halverson vomiting and coughing all night after receipt of Fluzone.

2. Mrs. Halverson's systemic inflammatory response affected her cardiac function

Dr. Stark opined, ". . . on January 9, 2014, the date of the vaccination, Mrs. Halverson's cardiac condition was stable, and the examination did not reveal signs of an imminent adverse event. Specifically, Mrs. Halverson did not have a displaced apical impulse, and she had normal heart auscultation, including normal S1 and S2, without murmurs, rubs, or gallops. Her heartbeat was regularly irregular." Pet. Ex. 18 at 3. He explained, "A person can have an atrial arrhythmia, which [Mrs. Halverson] did, occasionally, and can live and can thrive…A person can live with [atrial fibrillation], a person can do all his or her usual activities, it's very, very seldom fatal." Tr. 129-31. In addition to her atrial fibrillation, she also had insulin-dependent diabetes with chronic renal insufficiency, high cholesterol, obesity, and hypertension, as well as left bundle branch block and intermittent ventricular tachycardia. Pet. Ex. 20 at 2. "Together, these risk factors put Mrs. Halverson at extreme high risk for any external factor that could destabilize her heart rhythm, impair her heart function, or make her blood and platelets more prone to clotting." *Id*. Dr. Patel agreed, stating "[t]he elevated/altered cardiovascular parameters in a patient with diabetes and cardiovascular disease leads to catastrophic consequences and results in abnormal demand/supply of blood flow to the heart." Pet. Ex. 22 at 4.

Dr. Stark opined that Mrs. Halverson's underlying risk factors made her "far more vulnerable to the synergistic effect of platelet activation and autonomic dysfunction." Pet. Ex. 17 at 1. When asked what ultimately caused her cardiac arrest and death, Dr. Stark responded, "It was an acute coronary event causing a heart attack which caused her heart to stop…[d]ue to inflammation causing platelets to complete a blockage of her coronary artery, and the inflammation was due to a preceding flu immunization." Tr. 101. He referred to the arm pain and numbness that Mrs. Halverson complained of post-vaccination, explaining, ". . . females who are having heart attacks, often get arm numbness and don't get chest pain. [Mrs. Halverson] fits the pattern.…it is more likely than not that [Mrs. Halverson] was experiencing the beginning of a heart attack, at least before she collapsed." Tr. 97.

[49] *See supra* n.37.

Dr. Stark submitted medical literature indicating that in susceptible individuals, particularly diabetics, the flu vaccine can induce platelet activation, adrenergic predominance, and inflammatory reactions. Pet. Ex. 18 at 3; *see also* Pet. Ex. 10 (Study concluding "that influenza A vaccination in patients with type II diabetes induces, together with the expected inflammatory reaction, an increase in platelet activation and a cardiac sympathovagal imbalance").[50] He explained that, due to her co-morbidities, which included diabetes, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, and coronary artery disease with permanent defibrillator and reduced ejection fraction, Mrs. Halverson was extremely susceptible to "any external factor that could destabilize her heart rhythm, impair her heart function, or make her blood and platelets more prone to clotting." *Id*.; Pet. Ex. 20 at 2. "The pathophysiological link between the inflammatory and the cardiac autonomic responses to the vaccine are manifested by an increased risk of cardiovascular events and significant changes in heart rate variables." *Id*. at 3-4. Dr. Stark concluded that the "systemic inflammatory effects" from Fluzone exacerbated Mrs. Halverson's cardiac conditions and contributed to or caused her cardiac arrest. Pet. Ex. 17 at 2; Pet. Ex. 20 at 2.

3. Respondent submits that there is no evidence that Fluzone caused Mrs. Halverson to develop a systemic inflammatory response and/or a worsened cardiac condition

Dr. Rose agreed that, on the date of her vaccination, Mrs. Halverson was in relatively good health, although she complained of upper respiratory symptoms for three days. Resp. Ex. D at 3. In his opinion, there is nothing to suggest that Mrs. Halverson had hyperinflammation or any signs of chronically dysregulated inflammasomes. *Id*. at 8. According to Dr. Rose, the best support for petitioner's expert's suggestion of heightened chronic inflammation generated from Fluzone would be serial blood samples taken periodically after vaccination. *Id*. at 6. This was not done here and is rarely done on humans. *Id*. In Dr. Murphy's opinion, however, measurement of serum markers would not likely be helpful since patients with heart failure, renal failure, or diabetes may have elevated cytokine levels absent influenza vaccine. Resp. Ex. O at 4.

In lieu of Dr. Stark's theory that Fluzone caused out-of-control inflammation in Mrs. Halverson, resulting in platelet aggregation and adverse effects to cardiac autonomic function, Dr. Rose offered macrophage activation syndrome, a clinical condition marked by activation and expansion of the macrophages and other innate immune cells, as an example of a systemic cytokine response. Resp. Ex. D at 7. He stated, "These are systemic diseases involv[ing] multiple organs caused by dysregulated production of many pro-inflammatory cytokines." *Id*. In response, Dr. Stark stated that Dr. Rose mischaracterized his opinion. On the contrary, his opinion invoked "the well-recognized, enhanced inflammatory response that is characteristic following Fluzone immunization," but "in a highly susceptible individual, would be more than sufficient to trigger cardiac arrhythmia, congestive heart failure or cardiac arrest." Pet. Ex. 20 at 2.

Dr. Rose agreed that Mrs. Halverson's condition became worse after Fluzone. Tr. 301. He agreed that vomiting and severe cough were known adverse effects of Fluzone. Tr. 302. He stated that he could not rule out the possibility that her malaise, vomiting, catatonia, and other symptoms were due to Fluzone. Tr. 301. He noted the possibility that Fluzone could cause an enhanced

[50] *See supra* n.19.

systemic response in a person with an ongoing upper respiratory infection and agreed that an upper respiratory infection can induce an inflammatory response. Tr. 294, 309. Dr. Rose agreed that Mrs. Halverson's symptoms following receipt of the Fluzone vaccine "could be the result of an inflammatory reaction" but stated that it would not be the result of an immune response, which would take more time. Tr. 266. When asked if Mrs. Halverson developed SIRS, Dr. Rose responded that she had some changes that were associated with SIRS but not others, and it depended on the criteria used for SIRS. Tr. 277. In his opinion, he did not believe she suffered from SIRS. Tr. 278. Dr. Rose concluded that there is no evidence that a systemic event like SIRS caused heart failure in Mrs. Halverson. Resp. Ex. D at 7.

Dr. Murphy opined that, prior to her receipt of Fluzone, Mrs. Halverson "had really bad heart disease. She had a cardiomyopathy, which means the [heart] muscle wasn't squeezing well." Tr. 180. However, he also agreed that despite her health conditions, she was "doing pretty well." Tr. 180. He further agreed that Mrs. Halverson was "feeling a little bit crummy after the flu vaccine", and that she was sick and had symptoms that would be compatible with an upper respiratory tract infection. Tr. 199, 217. "Based on the record it probably was an upper respiratory infection, but…it could have been a heart failure exacerbation that wasn't fully recognized." Tr. 217. He stated, "[I]t would seem that she obviously was ill…she probably had some kind of an upper respiratory infection, but I can't exclude that it's something a bit more." Tr. 218. He also suggested that she may have had pneumonia. Tr. 181.

Despite the foregoing, Dr. Murphy concluded that there is "no convincing clinical evidence" to support that Mrs. Halverson had an inflammatory response following Fluzone. Resp. Ex. O at 3. When asked about Mrs. Halverson's symptoms of malaise, fatigue, vomiting, and catatonia in the days after receiving Fluzone, Dr. Murphy responded that those symptoms could be explained by a progression in her renal dysfunction, uncontrolled diabetes, or worsening heart failure. She did not meet the definition of SIRS. Tr. 198. He noted that Mrs. Halverson reported increasing shortness of breath prior to the administration of the Fluzone vaccine, and attributed it to a respiratory tract infection, an exacerbation of her heart failure, or a combination of both. Resp. Ex. A at 4. In Dr. Murphy's opinion, it was possible, but not probable, that the Fluzone vaccine given to Mrs. Halverson adversely affected her health. Tr. 201. "So my answer would be, there is a possibility, but I think it's improbable that the flu vaccine had anything to do with her eventual and tragic death." Tr. 201.

According to Dr. Murphy, Mrs. Halverson was a biologically fragile patient, so a specific cause of sudden deterioration is often multifactorial and difficult to determine. Resp. Ex. O at 3. She probably had coronary atherosclerosis, but due to her renal function, a coronary angiogram could not be performed, so while this diagnosis was suspected, it could not be proven. *Id*. Dr. Murphy opined that, due to a lack of testing, there was no evidence of inflammation in Mrs. Halverson's heart.

> …the possibility of idiosyncratic individual harm in a specific patient cannot be completely excluded. Short of an antemortem endocardial biopsy or postmortem histological examination of Mrs. Halverson's heart (which to the best of my knowledge did not occur), there is no scientific method based on my review of her

> clinical notes to reliably detect cellular inflammation in the heart muscle or inflammation in a coronary artery atherosclerotic plaque.

Resp. Ex. O at 3-4.

Dr. Murphy pointed to Dr. Stark's recognition of Mrs. Halverson's frailties, submitting that he was inconsistent when he referred to her being clinically stable and not at high risk for clinical deterioration. Resp. Ex. O at 2, citing Pet. Ex. 20 at 2. Dr. Murphy took issue with Dr. Stark's statement that Mrs. Halverson's medical problems were successfully treated for 65 years. *Id*. at 7. Dr. Murphy stated that patients with congestive heart failure have a five-year survival rate of about 50% unless a structural defect is identified and remedied. *Id*. He pointed out that her cardiologist noted her to have a "very brittle" cardiovascular system. *Id*.; *see also* Pet. Ex. 4 at 83. She also had chronic renal failure, which is associated with a significantly increased risk of mortality. *Id*.

Dr. Murphy admitted that, if he had been treating Mrs. Halverson, he would have done a chest x-ray when her symptoms did not improve following her appointment on January 9, 2014. Tr. 192-93. If she had been his patient, he would have told her to come back a week after the January 9, 2014 visit before giving her the flu vaccine. Tr. 194-95. Dr. Murphy explained, "I would feel more comfortable that this upper respiratory tract infection had blown over before I would give her the vaccine." Tr. 195. "I would prefer to vaccinate somebody in the whole of their health rather than vaccinating them when they have a concurrent infection going on." Tr. 195. "I'm not aware of data which says giving a flu vaccine to somebody with an upper respiratory tract infection is dangerous," but he agreed that studies of Fluzone have excluded patients with upper respiratory infections from participating. He agreed that traditionally, a child will not be vaccinated if he or she is ill. Tr. 196.

When asked if Mrs. Halverson's condition/death could have been a combination of her diabetes, her heart, other comorbidities, and the Fluzone vaccination, Dr. Murphy concluded, "I cannot separate out any one of those as specifically causal." Tr. 199-200.

5. *Althen* Prong 2/*Loving* Factor 5: Discussion

Petitioner testified that, in the days following her receipt of Fluzone, Mrs. Halverson suffered from severe cough, vomiting, shortness of breath, fatigue, weakness, and malaise. Tr. 11-16. Petitioner's testimony is corroborated by the medical records and the emergency room records, which reflect that petitioner reported that Mrs. Halverson had been suffering from an upper respiratory infection, malaise, weakness, decreased intake, cough, shortness of breath, nausea, vomiting, and congestion for the past few days. Pet. Ex. 9 at 16-17.

According to Drs. Patel, Stark, and Rose, a systemic inflammatory response is evidenced by fever, chills, muscles aches and pains, headache, fatigue, malaise, increased heart rate, and increased respiratory rate. Tr. 72, 114-15, 133-34, 263. The symptoms that Mrs. Halverson developed in the days following her receipt of Fluzone fit squarely within the clinical symptoms associated with SIRS.

All of the experts in this matter agreed that Mrs. Halverson had a fragile cardiovascular system, and that she had a URI at the time she received Fluzone. Pet. Ex. 17 at 1; Pet. Ex. 18 at 3; Pet. Ex. 20 at 2; Pet. Ex. 22 at 4; Resp. Ex. A at 3, 4, 22; Resp. Ex. O at 9; Resp. Ex. D at 3; Tr. 58, 101-02. Drs. Patel and Stark testified that the combination of Fluzone and the URI, in the setting of Mrs. Halverson's increased susceptibility to cardiac events, caused her cardiac arrest. Dr. Murphy conceded that he could not separate out her diabetes, cardiac issues, other comorbidities and the Fluzone vaccination as specifically causal. Tr. 199-200.

This case resembles *Shyface v. Sec'y of Health & Human Services*, in which Cheyenne Shyface was vaccinated with whole-cell DPT at the time he was beginning an *E. coli* infection. Both the DPT and the *E. coli* infection could and did cause a fever, which rose to 110 degrees, resulting in Cheyenne's death four days later. 165 F.3d. at 1345. Respondent defended the case and argued that the *E. coli* infection was the cause of his fever and death. Cheyenne's treating physician testified that both the vaccine and the infection were equally responsible for his fever and death. The Federal Circuit held that each of the two factors, the vaccine and the infection, was a substantial factor in causing the baby's very high fever and death and but for the vaccination, the baby would not have had the high fever and would not have died. *Id*. at 1353.

I find here that Mrs. Halverson's upper respiratory infection, her co-morbidities, and Fluzone were all substantial factors contributing to her death. But for Fluzone, Mrs. Halverson would not have died. Accordingly, petitioner has satisfied *Althen* prong 2/*Loving* factor 5.

C. *Althen* Prong 3/*Loving* Factor 6: Temporal Relationship

Dr. Stark stated that the "four-day proximate temporal relationship" supports his opinion that Mrs. Halverson's vaccine on January 9, 2013 "significantly aggravated her atrial fibrillation, myocardial infarction and death." Pet. Ex. 18 at 4.

Dr. Stark explained that Fluzone elicits an "enhanced systemic inflammatory response" which generally occurs three to seven days after immunization, the same length of time between Mrs. Halverson's receipt of Fluzone and her subsequent cardiac arrest. Pet. Ex. 19 at 1. At hearing, he discussed the amount of time it takes for an inflammatory response to develop following Fluzone. Dr. Stark testified, "…beginning at day three or three (sic) four [after vaccination], you are getting an inflammatory response and the effect on the heart is such that if your heart was jumpy to begin with, that you had extra heartbeats, you had arrhythmias, which are bad, jazzing up the heart by – with inflammation makes those extra beats be even more frequent and a rhythm is more likely." Tr. 93. He added, "The local inflammation [in the arm where the vaccine was injected] begins in 10 hours after the immunization, but the production of antibodies and inflammation goes seven, 10, 14 days." Tr. 93.

For support, Dr. Stark cited to the package insert for Fluzone, noting that the "label indicates that the vaccine may cause Guillain-Barre syndrome for up to 6 weeks after administration." Pet. Ex. 18 at 4, citing Pet. Ex. 31. Dr. Stark concluded, "It is well-established that reactions to the influenza vaccines manifest up to weeks after the administration of the vaccine and adverse events often manifest in a shorter timeframe." *Id*.

Dr. Rose testified that it takes four to six days for the immune system to generate antibodies to Fluzone. Tr. 259. He stated that a local reaction to Fluzone, evidenced by swelling and redness at the injection site, "will generally go for maybe two to four days, depending again on the intensity of the inflammatory response." Tr. 262. Dr. Rose did not address whether four days is an appropriate amount of time for a person to develop a systemic inflammatory reaction.

According to Dr. Murphy, the temporal relationship between Mrs. Halverson's receipt of Fluzone and subsequent cardiac arrest can be adequately explained by her history of long standing cardiac, diabetic, hypertensive and renal disease. Resp. Ex. O at 9. Dr. Murphy opined that congestive heart failure and atrial fibrillation are common diseases in the elderly "and would be expected to frequently occur proximate to influenza vaccination by chance alone." *Id*. at 8. According to Dr. Murphy, the coincidence of flu vaccination and heart failure or atrial fibrillation in the elderly population is so common that the "determination of a causal relationship. . . would be almost impossible." *Id*. He provided statistics in support of his opinion, stating that there are 5.7 million heart failure patients in the United States; about 50% of patients with heart failure die within 5 years of diagnosis. Resp. Ex. A at 4; Resp. Ex. G at 1.[51] Dr. Murphy estimated that a 50% mortality rate over five years is equivalent to about 500,000 deaths due to heart failure every year. Resp. Ex. A at 4. During the 2013-2014 flu season, 46% of people in the U.S. received the flu vaccine. Resp. Ex. F at 1. If 46% of heart failure patients were vaccinated, then about 230,000 vaccinated heart failure patients die annually. Resp. Ex. A at 4. By what he called a "back of the envelope calculation" from data of peer reviewed literature, Dr. Murphy stated that in "a 6-month window for influenza vaccination, the estimated number of US heart failure patients who will die within one week of influenza vaccination based solely on chance and not causally related to influenza vaccination is estimated at 8,000-9,000 annually." *Id*. Dr. Murphy did not submit any studies where individuals suffering from an upper respiratory infection who also had a fragile cardiovascular system received Fluzone without event.

Althen Prong 3/*Loving* Factor 6: Discussion

Mrs. Halverson had a URI when she received Fluzone on January 9, 2014. Later that evening, she began vomiting and developed a severe cough. On January 10, 2014, she had numbness and tingling in her arms, fatigue, malaise, weakness, and shortness of breath. She deteriorated and, three days later, suffered a cardiac arrest and died.

Petitioner's experts opined that there is a temporal relationship between Mrs. Halverson's receipt of Fluzone and her development of SIRS. Dr. Stark pointed to the Fluzone package insert, which, among other warnings, included the onset of systemic adverse events usually within three days of vaccination. *See* Pet. Ex. 31 at 3. Dr. Murphy did not address whether four days was appropriate for a systemic inflammatory response; rather, he viewed Mrs. Halverson's death four days after Fluzone as coincidental and solely due to her heart conditions. Dr. Rose did not discuss the length of time required for a systemic inflammatory reaction to develop, but he did state that it takes four to six days for the immune system to generate antibodies to Fluzone. This opinion implies that Mrs. Halverson's symptoms began too rapidly to be a response to her receipt of Fluzone. However, I have previously found that administration of a flu vaccine in the setting of a

[51] CDC Heart Failure Fact Sheet, filed as "Resp. Ex. G."

preexisting URI can cause an increased immune response resulting in a more rapid onset of symptoms, based on the concession made by respondent's expert in that case. *See Lehrman v. Sec'y of Health & Human Servs*., No. 13-901V, 2018 WL 1788477, at *19 (Fed. Cl. Spec. Mstr. Mar. 19, 2018) (Finding a temporal relationship existed between petitioner's flu vaccine and development of GBS symptoms within 24 hours, when the petitioner had recently suffered a URI at the time of his vaccination).

Furthermore, Mrs. Halverson's clinical course is analogous to that experienced by the vaccinee in *Bragg v. Sec'y of Health & Human Services*. In *Bragg*, the vaccinee "felt ill 30 minutes after receiving the flu vaccination. He never felt any better but continued to get worse until he died." 2012 WL 404773, at *26 (Fed. Cl. Spec. Mstr. Jan. 18, 2012). The special master found that there was a temporal connection between the vaccinee's flu vaccine and his development of SIRS:

> The timing is compelling in this case….When someone becomes ill with a vaccine injury and worsens day by day until he dies, a reasonable conclusion is that the immunologic challenge caused the illness.…In the instant action, the timing of decedent's onset of his mortal illness is consistent with systemic inflammation response syndrome, the response being to flu vaccination.

Id. at *26-27. Notably, the vaccinee's symptoms began shortly after vaccination and continued to progress until his death five days post-vaccination. *Id*. at *1. The timing of Mrs. Halverson's clinical course is very similar, with an already fulminating upper respiratory infection and an onset of vomiting, coughing, and progressive deterioration the day of vaccination, culminating in death four days later. Like the special master in *Bragg*, I find the timing of Mrs. Halverson's receipt of Fluzone and subsequent deterioration quite compelling. According to petitioner's experts, it is medically acceptable to infer a temporal relationship between Fluzone and Mrs. Halverson's development of SIRS and subsequent death. Respondent's experts did little to dispel petitioner's argument. Accordingly, petitioner has satisfied *Althen* prong 3/*Loving* factor 6.

D. *Loving* Factor 1: Mrs. Halverson's Condition Prior to Fluzone

As detailed in the facts section above, prior to her receipt of Fluzone, Mrs. Halverson had a host of co-morbidities. *See* Pet. Ex. 3 at 2-7; Pet. Ex. 4 at 7, 11; Pet. Ex. 7 at 1, 5. She also had a history of heart issues as documented at length throughout this Ruling. See Pet. Ex. 3 at 2; Pet. Ex. 4 at 27; Pet. Ex. 7 at 5, 24-29, 41, 91-92, 104, 154-55.

When she presented for placement of a permanent biventricular AICD in September of 2013, Mrs. Halverson's expected survival was greater than one year. Pet. Ex. 7 at 104. The AICD was recommended due to Mrs. Halverson's potential for sudden cardiac related to her episodes of ventricular tachycardia. *Id*. at 7-8.

As the medical records reflect, after placement of the AICD, Mrs. Halverson's health improved. She had more energy and wanted to walk more. Tr. 42. At a visit with Dr. Arluck in November of 2013, Mrs. Halverson reported that she no longer had nocturnal dyspnea but still had shortness of breath when walking. Pet. Ex. 6 at 19; Pet. Ex. 7 at 14. An echocardiogram showed that she had atrial and biventricular racing. Pet. Ex. 4 at 4. Petitioner recalled that petitioner saw

Dr. Arluck in December of 2013; he stated that Mrs. Halverson was "doing fine" and told her to return in four months. Tr. 9.

According to petitioner, Mrs. Halverson developed a slight cold around January 7 and 8, with cough, sneezing, and congestion. Tr. 8, 47. He did not recall her being fatigued or having shortness of breath or having a similar cold himself. Tr. 24-26.

Upon presenting to Dr. Sparagna on January 9, 2014, Mrs. Halverson was noted to have nasal congestion, a loose but non-productive cough, and a scratchy throat. Pet. Ex. 3 at 5. She reported "clogged" ears and difficulty hearing but no ear pain. *Id*. She complained of fatigue and was noted to walk with a cane for balance. *Id*. She did not have difficulty breathing at that examination. *Id*. Dr. Sparagna diagnosed her with an upper respiratory. *Id*. at 5, 7. She was administered a Fluzone vaccine. *Id*. at 2.

E. *Loving* Factor 2: Mrs. Halverson's Condition Following Fluzone

Petitioner stated that Mrs. Halverson experienced "rapid degeneration" following Fluzone; he recalled that she began vomiting later the day of the vaccine, after dinner, and continued to vomit through the night, culminating in dry heaves the following morning. Tr. 11, 28. According to petitioner, Mrs. Halverson had started to lose her voice and her hearing. Tr. 12. Her arms were numb and tingling, "like when your foot goes to sleep." Tr. 12. Petitioner described her as "zombie-like," with "less than half of her normal energy." Tr. 12, 14.

Mrs. Halverson deteriorated in the following days and petitioner finally convinced her to go to the hospital on January 13, but she wanted to change her clothes first. Tr. 15-16. She collapsed while in the bathroom and could not be resuscitated. Tr. 16; Pet. Ex. 9 at 16-17; 20-21. Her immediate cause of death was listed as cardiac arrest due to ischemic heart disease. Pet. Ex. 2 at 1.

F. *Loving* Factor 3: Significant Aggravation vs. Natural Progression of Disease

Dr. Murphy submitted that Mrs. Halverson's death was the result of the natural progression of her severe cardiac disease combined with her comorbidities. In his opinion, Mrs. Halverson suffered from a "constellation of medical conditions" which placed her "at high risk of sudden cardiac death without the need to invoke a vaccine specific etiology for her untimely death." Resp. Ex. A at 3. In his opinion, her sudden death was typical of the natural course of the patient with severe structural cardiac disease with recurrent episodes of heart failure and poor left ventricular function compounded by insulin-dependent diabetes and chronic renal failure. Resp. Ex. A at 4.

1. Respondent submits that Mrs. Halverson was in poor cardiac condition prior to Fluzone

Dr. Murphy thoroughly discussed Mrs. Halverson's medical history in his reports and at hearing. He noted that she likely had underlying suspected coronary artery disease based on her history of smoking, insulin-dependent diabetes, hyperlipidemia, hypertension, and renal failure. Resp. Ex. A at 3. Dr. Murphy clarified that she was only "suspected" to have coronary artery disease because her doctors did not do a coronary angiogram, which, in Dr. Murphy's opinion,

"you would typically do [here]." Tr. 166; Resp. Ex. A at 3. Dr. Murphy suggested that Mrs. Halverson's doctors "were afraid that they would precipitate a further decline in her kidney function, because the x-ray dye tends to be toxic to the kidneys." Tr. 166.

A nuclear stress test in 2013 showed that Mrs. Halverson had abnormal ventricular function with multiple regional wall motion abnormalities but no definitive evidence of myocardial ischemia. Resp. Ex. A at 3. According to Dr. Murphy, this did not exclude occult coronary artery disease. *Id*. She had a permanent pacemaker due to heart block in 2001 and biventricular pacemaker/defibrillator in 2013. *Id*.

Dr. Murphy noted that, after Mrs. Halverson received the AICD, her ejection fraction improved, though it was still below normal. Tr. 168-69. It went from 25 to 30 percent up to 45 percent. Tr. 172-73. She had an EKG on December 12, 2013 which showed an ejection fraction of 45 to 50 percent, "which is much better than the 25 to 30 percent previously." Tr. 183. According to Dr. Murphy, Mrs. Halverson had "a reasonably good response" to the AICD. Tr. 183. He added, "[T]he ejection fraction is useful, but there are limitations to how effective it is. And just because your ejection fraction is normal doesn't mean that you're okay." Tr. 169. Dr. Murphy conceded that, "[T]he fact that her ejection fraction got better would reduce the risk of sudden death." Tr. 177.

Mrs. Halverson had an echocardiogram on December 12, which showed "abnormal diastolic function, which is typical of patients who have long-standing hypertension, and patients with kidney disease." Tr. 185. Dr. Murphy estimated that the abnormal diastolic function was long-standing. Tr. 185. He observed that her pulmonary valve, aorta, and pericardium were normal. Tr. 186. He further noted that she had signs of an old heart attack. Tr. 186.

According to Dr. Murphy, it is possible but unproven that Mrs. Halverson may have had a myocardial infarction. Resp. Ex. A at 22. In his opinion, it is more likely that she had ventricular fibrillation secondary to her underlying ventricular dysfunction and congestive heart failure. *Id*. "A relatively normal clinical examination does not exclude the possibility of sudden cardiac arrhythmia in a very high-risk patient, such as Mrs. Halverson." *Id*. He noted that the rhythm strip from her ER admission showed ventricular fibrillation. *Id*.; *see also* Pet. Ex. 9 at 8. In Dr. Murphy's opinion, "She died of a cardiac arrest" caused by ventricular fibrillation. Tr. 211, 222.

Additionally, Dr. Murphy added that Mrs. Halverson was short of breath prior to vaccination, "which was probably an exacerbation of her congestive heart failure. Thus she was not [in] stable condition prior to her vaccination." Resp. Ex. A at 21. The medical records indicate that Mrs. Halverson routinely reported shortness of breath beginning in 2010. *See* Pet. Ex. 4 at 44-45, 59-60.

2. Respondent submits that Mrs. Halverson was at a high risk for sudden death

In Dr. Murphy's opinion, Mrs. Halverson was at a high risk for sudden death prior to her receipt of the Fluzone vaccine. At hearing, Dr. Murphy explained that 50 percent of patients with heart failure die within five years. According to Dr. Murphy, Mrs. Halverson's heart failure began

"several years" before her death in 2013 and was the natural progression of disease for a person with heart failure. Tr. 202.

To support his opinion, Dr. Murphy offered multiple statistics on heart failure. He explained that sudden death is common in patients with congestive heart failure, occurring at a rate of six to nine times that of the general population. Resp. Ex. A at 5. Heart failure contributes to 287,000 deaths a year; in 2009, one in nine deaths was attributed to heart failure. *Id*. 50% of patients who develop heart failure die within five years. *Id*. More than five percent of people age 60 to 69 have congestive heart failure, and 10 per 1,000 people older than age 65 have congestive heart failure. *Id*. Heart failure is responsible for 11 million medical visits each year and more hospitalizations than all forms of cancer combined. *Id*. One-fifth of all hospitalizations have heart failure as the primary or secondary diagnosis. *Id*. Based on these statistics, he was confident that Mrs. Halverson had a high risk of sudden death prior to receiving the Fluzone vaccine and that her sudden death four days after Fluzone did not imply a causal relationship. Resp. Ex. O at 9.

Dr. Murphy further submitted that Mrs. Halverson had an expected five-year mortality of 50 to 70% based on end stage kidney disease. Resp. Ex. A at 4. She was given a diagnosis of stage IV kidney disease in 2011. Pet. Ex. 4 at 37-38. According to her records, she had not progressed to stage V, or "end stage" kidney disease, which requires dialysis.[52] The experts did not discuss whether renal failure could cause cardiac arrest, but Dr. Murphy stated that one possibility for Mrs. Halverson's symptoms following Fluzone was progression of her renal dysfunction. Tr. 198. However, there are no medical records indicating that Mrs. Halverson's renal disease was worsening at that time.

Dr. Murphy concluded, "I think the cause of her death was the natural history of her multiple comorbidities, particularly her heart disease, her renal failure, her diabetes, and more likely than not, that was the cause of this poor lady's death." Tr. 202.

Dr. Patel agreed that heart failure and renal failure can also cause immunostimulation. Tr. 66. However, he noted that Mrs. Halverson appeared to improve following the implantation of the AICD and her deterioration occurred shortly after vaccine administration. Tr. 66-67.

In response to Dr. Murphy's opinion that Mrs. Halverson's death was secondary to her long term underlying cardiac risk factors, Dr. Stark pointed out that for 65 years she had been successfully treated for each of her medical problems. Pet. Ex. 19 at 1.

3. *Loving* Factor 3: Discussion

While Mrs. Halverson suffered from a number of conditions, including diabetes, renal failure, atrial fibrillation, and congestive heart failure, she had been living with these conditions for years. She worked to maintain her health, regularly presenting for care to her cardiologist, primary care physician, and other specialists. Following the implantation of an AICD in September of 2013, Mrs. Halverson had more energy and was more active. Approximately one month before she received the Fluzone vaccine, she had an echocardiogram, which showed that her left

[52] "Stage 5 [of chronic kidney disease] has a GFR below 15 (end-stage renal disease), and patients require dialysis." *Chronic kidney disease*, DORLAND'S at 530.

ventricular systolic function had markedly improved since the last study. Her cardiologist said she was "doing fine." Overall, it appears that her heart condition, while serious, was stable.

When she presented to Dr. Sparagna on January 9, 2014 with an upper respiratory infection, Mrs. Halverson reported nasal congestion, a loose but non-productive cough, scratchy throat, numbness in her feet, fatigue, and difficulty hearing; she did not complain of vomiting, severe cough, weakness, or malaise. Pet. Ex. 3 at 5-7. She was not "zombie-like." She walked into the doctor's office of her own accord and went to the pharmacy with petitioner to purchase the medication prescribed. Her health took a rapid and markedly devastating turn that evening after receiving the Fluzone vaccination. Tr. 10-17; Pet. Ex. 9 at 16-17.

Dr. Stark and Dr. Murphy agree that Mrs. Halverson's immediate cause of death was cardiac arrest but differ as to the cause of said cardiac arrest. In Dr. Stark's opinion, the combination of Fluzone, a high-dose flu vaccine, and URI caused Mrs. Halverson to develop SIRS, which strained her heart and caused cardiac arrest. According to Dr. Murphy, Mrs. Halverson's cardiac arrest occurred as the natural progression of her preexisting heart conditions. Dr. Murphy based this opinion on the statistical likelihood that Mrs. Halverson would die within five years of being diagnosed with congestive heart failure. However, the Federal Circuit has rejected arguments put forth by petitioners which rely heavily on statistical likelihood as proof of causation. *See, e.g., Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1363 (Fed. Cir. 2019) (rejecting petitioners' theory due to expert's reliance on statistics that a brainstem defect is found in 50-70% of SIDS cases, and that, given these statistics, the vaccinee likely had a defect); *Knudsen*, 35 F.3d at 550 (rejecting the government's alternative cause theory based on "[t]he bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies"). While I acknowledge that the burden here lies with petitioner rather than respondent, the Federal Circuit has rejected arguments relying on statistics from both petitioners and respondent. Based on the totality of the circumstances, I find petitioner's expert more persuasive.

Based on the above, petitioner has proffered preponderant evidence that Mrs. Halverson's death was not the natural progression of her heart disease, but rather a combination of the Fluzone and her upper respiratory infection that significantly aggravated her preexisting heart disease, resulting in her death.

G. Respondent's Burden to Show Unrelated Factors

Because petitioner has established a prima facie case of causation/significant aggravation, he is entitled to compensation unless respondent can show by the preponderance of the evidence that Mrs. Halverson's injury was caused by a factor unrelated to the Fluzone vaccine. *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). To meet this standard, respondent must "present sufficient evidence to prove that the alternative factor was the sole substantial factor in bringing about the injury." *Id*. at 1368. The Vaccine Act limits the scope of unrelated factors by excluding any "idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition." § 13(a)(2)(A). "In other words, alternative causes that are 'idiopathic, unexplained, unknown,

hypothetical or undocumentable' cannot overcome a petitioner's prima facie case." *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1357 (Fed. Cir. 2010) (quoting § 13(a)(2)(A)).

As discussed above, respondent submitted that Mrs. Halverson's death was the result of her preexisting heart disease, which predisposed her to sudden cardiac death. Dr. Rose testified that he had "no theory to explain her death." Tr. 299. Dr. Murphy conceded that he would not have vaccinated her if she was his patient but would have waited a week and reexamined her before giving the vaccination. While refusing to concede Fluzone's role in Mrs. Halverson's death, Dr. Murphy agreed that he could not parse out among her comorbidities and Fluzone any one thing to attribute her death to. Having determined that Mrs. Halverson's death was the result of a significant aggravation of her cardiac condition by Fluzone rather than the natural progression of her condition, I find that respondent has failed to demonstrate that Mrs. Halverson's preexisting heart disease was the sole substantial factor in bringing about her death on January 13, 2014.

VII. Conclusion

I extend my sympathies to petitioner for the loss of his wife. Upon careful evaluation of all of the evidence submitted in this matter, I find that petitioner has established entitlement to compensation under the Vaccine Act. Accordingly, this case shall proceed to damages. In matters such as this one, where the vaccinee is deceased at the time of a compensation award, the estate can recover the death benefit of $250,000 as well as "pain and suffering and emotional distress from the time of the injury until the date of death." *Tembenis v. Sec'y of Health & Human Servs.*, 733 F.3d 1190, 1193 (Fed. Cir. 2013) (citing *Zatuchni v. Sec'y of Health & Human Servs.*, 516 F.3d 1312, 1318-19 (Fed. Cir. 2008) (discussing damages available to a petitioner's estate where the petitioner had established vaccine-related injuries and vaccine-caused death).

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master